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NATIONAL CANCER INSTITUTE

ANNUAL REPORT

October 1, 1977 through September 30, 1978

Part V

DIVISION OF CANCER RESEARCH RESOURCES & CENTERS

US NATIONAL CANCER INSTITUTE
" Report of Program Activities
DIVISION OF CANCER RESEARCH RESOURCES AND CENTERS

ANNUAL REPORT

October 1, 1977 through September 30, 1978

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OFFICE OF THE DIRECTOR

In January 1978 the Director, NCI, announced plans to reorganize the National Cancer Institute. These plans called for transferring all program administration from the Division of Cancer Research Resources and Centers (DCRRC) to other Divisions of the Institute. The plans also called for transferring responsibility for all peer review functions from other Divisions to a renamed DCRRC.

Because the reorganization will not be fully accomplished until late in the fiscal year, this annual report remains in the format of the programs formerly administered within DCRRC.

Traditional Research Programs

The traditional research programs of DCRRC supported investigator-initiated and investigator-conceived research by awarding regular project research grants and program project research grants. These programs encompassed carcinogenesis, drug development and pharmacology, epidemiology, tumor biology, viral oncology, immunology, diagnosis and detection, clinical oncology, radiation therapy, and radiation biology and physics.

Organ Site Research

The National Organ Site Cancer Program extends the reliance on investigator initiatives to research program planning and administration in National Organ Site Cancer Projects. There are National Organ Site Cancer Projects for Bladder, Large Bowel, Prostatic, and Pancreatic Cancer. In each case, NCI has delegated many administrative and scientific responsibilities to a non-NCI National Project Director who is advised by a working cadre of scientists from a number of research institutions. National projects are planned and targeted, but they rely on investigator initiatives to fulfill their targeted research programs.

Manpower Programs

The Institute assures the development of cancer research talents and clinical cancer expertise in its Research Manpower Programs and its Clinical Cancer Education Program. These endeavors encourage the initiatives of the Nation's scientists, teachers, and educators by accepting unsolicited applications, and by identifying innovative cancer research training and cancer education through peer review. The Research Manpower Programs provide support for training in the many laboratory and clinical research disciplines relevant to cancer cause and prevention, cancer detection and diagnosis, and cancer therapy and restorative care. Research training initiatives are supported by Institutional and Individual Fellowship Awards as well as by Research Career Development Awards. The Clinical Cancer Education Program provides grants to support improved cancer teaching primarily in institutions which provide education for physicians and dentists. The Program's goal is to provide future health professionals who are properly educated to provide superior care and treatment to cancer patients.

Research Facilities

The Research Facilities Construction Program is devoted to establishing and expanding cancer research facilities in the United States. The Program's primary concern is the development of environments appropriate for independent initiatives in cancer research.

Cancer Centers

The Cancer Centers Program was the first to be affected by the reorganization plans. It was transferred to the Office of the Director, NCI, and Dr. William Terry was named Acting Associate Director for Cancer Centers. During the year, the Centers Program completed its evaluations of the comprehensiveness of NCI-designated centers. At its May 1978 meeting, the National Cancer Advisory Board recommended to the Director of NCI that the Cancer Center of Metropolitan Detroit be recognized as comprehensive. This would bring the total number of recognized comprehensive cancer centers to 20.

Cancer Research Emphasis Grants

The Division continued to coordinate NCI's Cancer Research Emphasis Grants (CREG). DCRRC provided guidance in policy and procedures for the NCI Divisions that use CREG. Cancer Research Emphasis Grants are solicited by Requests for Applications (RFA's) which designate the research desired but leave approaches and methodologies to the scientists who apply. The following table summarizes CREG awards made in fiscal year 1978.

CANCER RESEARCH EMPHASIS GRANTS

FISCAL YEAR 1978
(DOLLARS IN THOUSANDS)

NCI DIVISION	FY 1978 NO.	FY 1978 Amount
DCBD	7	$ 650
DCCP	64	5,618
DCT	21	3,181
TOTALS	92	$9,449

Young Investigators Awards

The first NCI Young Investigators Awards were funded during fiscal year 1978. These awards provide a maximum of $25,000 a year for up to three years for young investigators to initiate independent research. Thirty-two awards were made at a total cost of $1,064,000.

BUDGET

Funds available to support the programs of DCRRC in fiscal year 1978 amounted to $366,721,000. The distribution of those funds was as follows:

BUDGET DISTRIBUTION

FISCAL YEAR 1978
(Thousands of Dollars)

PROGRAM	$	$
REGULAR		
Traditional	$149,094	
Conference Grants	1,800	
Young Investigator Awards	1,064	
Scientific Evaluation	822	
Subtotal		$152,780
CENTERS		
Cancer Center Support Grants	60,250	
Exploratory Projects	700	
Clinical Cancer Patient Data System	1,650	
Subtotal		62,600
PROGRAM PROJECTS	85,423	85,423
RADIATION DEVELOPMENT	4,150	4,150
ORGAN SITE		
Bladder	4,370	
Large Bowel	5,472	
Prostate	4,316	
Pancreas	1,980	
Subtotal		16,138
CAREER		
RCDA	3,777	
RCA	240	
Subtotal		4,017
CLINICAL EDUCATION	9,450	9,450
FELLOWSHIPS	19,886	19,886
TRAINING		
Graduate	233	
Clinical	44	
Subtotal		277
CONSTRUCTION	12,000	12,000
TOTAL		$366,721

The Division made 3,025 awards and 328 supplements. The following table shows how the awards were distributed among noncompeting projects, competing renewals, new projects, and supplemental requests. The table also compares the amounts requested with the amounts approved and awarded.

FISCAL YEAR 1978

DISTRIBUTION OF AWARDS
(DOLLARS IN THOUSANDS)

	REQUESTED		RECOMMENDED		AWARDED		UNFUNDED	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
TYPE 5 (non-competing)	1,947	$223,566	1,947	$223,566	1,947	$223,566	0	$ 0
TYPE 2 (competing renewals)	862	220,733	734	109,824	375	71,676	359	38,148
TYPE 1 (new)	2,301	362,872	1,731	121,411	703	53,402	1,208	68,009
TYPE 3 (supplement)	(100)	19,411	(345)	19,049	(324)	18,077	(21)	972
TOTALS	5,110	$826,582	4,412	$473,850	3,025	$366,721	1,387	$107,129

The Cooperative Minorities Program

The Cooperative Minority Biomedical Program, which was approved by the National Cancer Advisory Board in March 1975, represents a collaborative effort by the National Cancer Institute to implement and foster cancer research through two established minority programs: the Minority Biomedical Support Program (MBS) of the Division of Research Resources and the Minority Access to Research Careers Program (MARC) of the National Institute of General Medical Sciences. Specifically, the National Cancer Institute provides funds and programmatic advice to support meritorious research and training grants that have an impact on the overall mission of the National Cancer Program in either of these programs. The NCI also provides a professional position to each program in support of its activities.

Both the MBS and MARC program proposals are reviewed by the parent Division or Institute with the possible participation at all levels of NCI staff (primarily the coordinating executive secretary of the CMBP) on applications with scientific research components of interest to the NCI. The DRR or NIGMS reviews are subsequently evaluated by NCI's CMBP which considers both merit and programmatic significance. The CMBP recommends NCI funding for those parts of approved applications which are judged meritorious and relevant. In fiscal year 1978, the NCI provided $990,000 to fund, in whole or in part, 34 applications in the MBS program. This constitutes 51 percent of the funding and 46 percent of the applications supported through the collaborative mechanism. Four other NIH Institutes also contribute through collaborative agreements with DRR.

The MARC program became operational during fiscal year 1978; therefore, NCI participation in this program covers only a portion of the year. Nine fellowships were funded in fiscal year 1978 using NCI-transferred funds.

OFFICE OF PROGRAM PLANNING

The Office of Program Planning is located in the Office of the Director, DCRRC, and is responsible for the planning and evaluation of grant-supported programs administered by the Division.

The Office of Program Planning (OPP) integrates data from various sources within the Division in order to establish a broad overview of past trends and present and future needs. It also serves the National Cancer Institute (NCI) as a whole by maintaining a close working relationship with the Office of Program Planning and Analysis (OPPA) in the Office of the Director, NCI.

Recent Studies

The Office of Program Planning continues to work closely with DCRRC scientific and management staff in assessing program area needs and in undertaking special studies on issues and information of importance to the NCI. Effective program planning requires a careful analysis of past policies and historical data which can be utilized in formulating programs for the future. Toward this end, the OPP has been involved in several significant special studies during the past year, including:

- Age of Investigators Analysis - To test the frequent assertion that older, more experienced principal investigators have a distinct advantage in competing for grants in the peer review system. The study found that young investigators (those 35 years of age or less) are not discriminated against in the review process and have, in fact, fared significantly better than their older colleagues in terms of recommendation and award rates.

- Analysis of Conference Support - To consider the view that informal conferences and workshops are faster, more effective methods of information transfer than traditional publications. A subsequent purpose of the study was to analyze NCI's recent conference activity in terms of number, size, cost, area of cancer activity, and relation to conference support by NIH as a whole. The results were prepared in narrative and graphic form, and (in keeping with the study described above) included a discussion of the unique opportunities that such symposia afford for younger investigators.

- Changes in Research Direction Since Passage of the National Cancer Act - To collect and analyze data on principal investigators whose support switched from other NIH institutes to the NCI following the 1971 Cancer Act. Grant titles and project descriptions of the same scientists for fiscal years 1968-71 and 1972-74 were compared, to ascertain if any significant change in research direction occurred. This study will provide one example of the extent to which the influx of funds to one disease category of biomedical research is accompanied by an increase in interested researchers and a requisite modification of scientific thrust.

- Length of Awards and Frequency of Review - In response to the concern expressed at the May 1978 meeting of the National Cancer Advisory Board. The concern was that shorter grants (nearly four-fifths of all NCI competing research awards are for a period of 3 years) are placing a severe strain on the grant process due to the increased frequency of application and review. The study will analyze whether lengthy awards in the past correlated with the best priority scores. This would, after all, be the only acceptable justification (i.e., preserving the integrity of scientific merit) for approving longer awards.

In addition, the OPP prepared and presented its annual, detailed Report on Grant-Supported Research Programs of the NCI (featuring charts and tables reflecting funding trends and current status of all grant-supported activities), as well as an Orientation of the National Cancer Advisory Board book to acquaint incoming NCAB members with the NIH and NCI and their role in the peer review process.

To help fulfill many needs of the Division, the OPP administers and manages contracts with outside firms and cooperates with the OPPA in several other contract-supported studies. Some tasks accomplished with the aid of these contracts follow.

Evaluation of Impact of HSA and State Agency Regulatory Functions on NCI/NIH Extramural Programs

The OPP led a study to review and evaluate the impact of the National Health Planning and Resources Development Act of 1974 (P.L. 93-641) on the NCI and NIH. This Act created new regulatory requirements which have implications for both NIH and its grantees and contractors. The legislation gives health systems agencies (HSA's) across the country review functions which may impact on NIH projects involving:

- development, expansion, or support of health resources (i.e., services, manpower, and facilities);
- capital expenditures related to development of or changes in health-care facilities and services;
- increase, conversion, or relocation of beds; and
- new health services.

Because P.L. 93-641 is being implemented in phases, its potential impact on NIH is developing incrementally as different sections of the law come into effect. Continuing efforts are necessary, therefore, to assist NIH staff and constituents in understanding the legislation's impact at each stage of implementation, and to determine what actions, if any, must be taken to comply with the law.

During the fiscal year 1977 an analysis of the health planning legislation and strategies for dealing with the requirements of P.L. 93-641 was prepared. NIH program directors were interviewed to determine which extramural activities would be most affected by HSA review. The analysis includes an examination of the NIH grant and contract processes to develop recommendations for a system to screen incoming applications and proposals for compliance with HSA regulatory requirements. Possibly the most critical task is the preparation of a document which will explain the unique needs and concerns of research investigators and institutions to the health planning agencies. This document will serve as the basis for any future local or state review of NIH grant applications and proposals.

During fiscal year 1978, an analysis was undertaken of the proposed regulations (NPRM) governing HSA review of certain proposed uses of Federal health funds. This analysis included the preparation of a document which identified and explained areas of concern for the NCI and its constituents. This document was subsequently shared with the Comprehensive Cancer Centers to assist them in preparing public comments for submission to the Bureau of Health Planning and Resources Development, HRA.

A draft set of instructions was developed for inclusion in grant applications which would explain the review requirements of HSA's and outline the compliance procedures to be followed by applicants. Additionally, a manual is being developed which will present an overview of NIH to local and state health planning agencies. This manual, which reviews the enabling legislation for the B/I/D's, the organization of the NIH, and its missions, objectives and programs, is intended to familiarize HSA's and State Agencies with the nature of NIH-supported activities and the unique needs of research institutions.

It is anticipated that a report will also be completed which will address the issues and problems of HSA review of biomedical research projects. General as well as specific examples of problem areas will be drawn from experiences of current NIH grantees. Recommendations will be developed to focus on potential areas for effective coordination and interfacing between cancer centers and local/state health planning agencies.

Patient Management Study

An ongoing study emphasizes the development of a methodology for documenting current patient management practices in institutions treating cancer patients. The methodology is also designed to aid in measuring the rate at which new research knowledge is translated into cancer patient care. The study relies upon:

1. Consensus on parameters of sound cancer patient management practices by physicians recognized nationally as experts in their specialties.

2. The use of nonphysician personnel to collect and process data.

3. The use of the hospital inpatient medical record as the data source.

More than 50 parameters of sound cancer patient management have been established among five categories: 1) early diagnosis and screening; 2) staging and extent of disease; 3) completeness and thoroughness of workup; 4) identification of prognostic factors influencing response to therapeutic regimens; and 5) documentation of treatment.

Based upon encouraging results in a preliminary field trial, efforts during the past year focused on testing the parameters for seven disease sites (breast, cervix, colon, head and neck, lung, Hodgkin's disease, and melanoma) in three institutions: 1) a community hospital, 2) a hospital affiliated with a clinical cancer center, and 3) a hospital affiliated with a comprehensive cancer center. In addition, three types of nonphysician personnel were used as medical records abstractors-- a registered nurse, an accredited records technician, and a tumor registrar.

Results demonstrated the potential of the methodology to:

1. Identify patient management changes over time within an institution.
2. Identify the time of adoption of certain techniques within given institutions.
3. Detect patient management differences among institutions over time.
4. Illustrate patient management similarities among institutions over time.

Additional evaluation studies are planned in order to validate the above observations and to establish statistical reliability and validity of the test instruments.

RESEARCH ANALYSIS AND EVALUATION BRANCH

The Research Analysis and Evaluation Branch serves as a major source of scientific information on NCI-supported research projects. Members of the Branch analyze and index the scientific content of all grants awarded by DCRRC, all NCI contracts, and all NCI intramural projects. They disseminate this information throughout NCI--to the other Divisions, the Office of Cancer Communications, Financial Management Branch, Program Analysis and Formulation Branch, and the International Cancer Research Data Bank, to other NIH organizations such as the Research Documentation Section and the Research Analysis and Evaluation Branch of the Division of Research Grants, to other NIH Institutes, and to other Government and private organizations. Staff members also compare pending grants and contracts with existing NCI-supported projects at the same institution to assure that there is no overlap or duplicated support for a research project.

As a result of the reorganization of NCI initiated in fiscal year 1978, the DCRRC program directors have been transferred to other NCI Divisions. This decentralization of personnel will make communication more difficult, and the Branch anticipates additional responsibilities for coordinating information about NCI-supported research.

As part of an Institute-wide effort to improve communications, the Branch Chief has been participating in NCI's Working Group on Information which was established by the director and has representatives from all the NCI Divisions. It was formed to organize scientific and technical information resources in order to:

1. improve coordination that would benefit research in the different Divisions and programs;
2. expose resources hidden in programs or Divisions that would be useful for education, research, or patient care;
3. establish conduits for information exchange on a routine basis;
4. provide better access to the content and purpose of various programs and projects; and
5. generate closer ties with bench scientists who are important sources of information.

Computer Information System

The Branch has continued to prepare data on funded NCI grants for the automated computer Grants Elements Network-Internal Users System (GENIUS), which became operational in July 1975, replacing the edge-punched McBee card system. Scientific data for each grant are indexed according to pertinent terms from a list of fixed terms compiled by the Branch, and according to specific key words or phrases provided by the indexer. In this way each grant is described concisely for input into the computer. The data can then be retrieved in a variety of formats in order to respond to inquiries and prepare reports.

In addition to the scientific indexing prepared by the Branch, two other types of data are available from the system. These include administrative data obtained from the Division of Research Grants' IMPAC System and Smithsonian Science Information Exchange (SSIE) abstracts supplied by the applicants.

When completely operational, the Grants Elements Network-Internal Users System will include data from five separate computer information storage files: (1) active research grants file with its companion history file of terminated grants, (2) unfunded grants, (3) active contracts, (4) intramural research projects, and (5) training programs. All scientific and administrative data on the active and history files and the intramural research file, except for the SSIE abstracts, are searchable on the computer. The unfunded grants file consists of disapproved and approved-but-not-funded grants for the past two years. This file contains only administrative data from IMPAC plus birth dates of the principal investigators. The project title, program area, and study section are the only points of access to scientific information on these projects.

The intramural research project file was added to the GENIUS system and became operational during this fiscal year. It is anticipated that an active contracts file will become operational in fiscal year 1979 and a training file by fiscal year 1980.

About 80 percent of the active grants, including new proposals and type 2 requests for continuing support, and 50 percent of the intramural research projects have been entered into the system. GENIUS is maintained and operated solely by the Branch, which is greatly indebted to the NIH Division of Computer Research and Technology (DCRT) for help in developing and implementing the system.

The system is used daily to answer requests for information on all areas of NCI-supported research. Records indicate that over the course of the past year the workload has markedly increased, the number of requests having more than doubled compared with the previous year. Some of these requests have involved supplying information to help develop specific requests for contract proposals. The requests cover a wide range of topics, such as the following:

1. effects of nonionizing radiation in the microwave range;
2. saccharin in relation to bladder cancer;
3. cryopreservation for blood components;
4. marijuana for supportive care of cancer patients;
5. marine organisms as a source of chemotherapeutic agents or as a research tool;
6. regeneration and cancer;
7. DNA repair;
8. environmental carcinogenesis;
9. computerized tomography; and
10. research by specific investigators.

Literature Surveillance

Published results are monitored through the Branch's literature surveillance program. About 300 major medical and scientific journals are scanned to identify those papers resulting from NCI grant-supported research. These references, and additional references obtained from reprints submitted by grantees, are arranged according to DCRRC program areas and the list is issued monthly with a subject and author index as the NCI Grant-Supported Literature Index.

The Index is the most complete record available of accomplishments of the total extramural research grant program and is entered into a computer searchable system. In calendar year 1977, about 5906 articles, representing the work of 11,037 authors, appeared in the Index.

Other Branch Activities

Narrative reports on selected areas of cancer research are prepared by the Branch at the request of DCRRC staff or at the initiative of Branch scientific staff members. A report prepared during the past year is entitled "Flow Microfluorometry: A Major Tool for Biomedical Research."

During the past year most members of the Branch took computer courses offered by DCRT. Such courses allow the staff to work more efficiently and to communicate more effectively about all aspects of the computer systems.

To alleviate the mass of paper resulting from the use of computers, the staff selected certain printouts to be put on microfiche, and recently purchased two microfiche readers. The use of microfiche has increased the efficiency of many daily activities and has relieved congested work space.

The Branch maintains regular liaison with other Divisions of NCI. Extra copies of grantees' reprints are sent to each Division, as are copies of the SSIE abstracts for all grants. SSIE abstracts of grants concerned with specific research areas are sent on a regular basis, upon request, to NCI staff such as members of the Breast Cancer Task Force and the Laboratory of Toxicology.

Staff members also serve on Division and Institute committees that attempt to foster better communications about NCI-sponsored research in areas judged especially significant to the National Cancer Program. Two such committees are the Steering Committee of the Breast Cancer Task Force and the Office of Cancer Communications' Ad Hoc Group on Cancer Information Clearinghouse Operations.

The Branch provided information for use in selecting a contractor to evaluate existing science information systems within the NCI in terms of their content, quality, capabilities, and usage. Eight systems will be evaluated, including those of the Research Analysis and Evaluation Branch.

REVIEW AND REFERRAL BRANCH

The Review and Referral Branch is responsible for (1) internal NCI program assignment of all grant applications referred to DCRRC; (2) assignment of grant applications for program project, core, construction, and other large instrument or special purpose grant applications to appropriate NCI review committees; (3) scientific merit review of the applications noted under (2) above; and (4) preparation of summary reports of the recommendations and evaluations of each committee review and of each site visit. This involves formulating goals, criteria, and strategy to meet these goals, as well as managing the activity. The latter includes analyzing, evaluating, and reporting. The Branch also serves as liaison between the Division of Cancer Research Resources and Centers and the Division of Research Grants, NIH .

The Review and Referral Branch provides initial peer review for large-scale multidisciplinary research projects (program projects) intended to generate knowledge of cancer--its biology or control. These applications are divided for review according to their major emphases, into either clinical or basic science proposals. The Branch also provides initial peer review of proposals for indirect support of research at Cancer Research Centers through core funding of administrative costs and services. Such services might include computer use, biostatistics information, cell-culture maintenance and evaluation, and routine biochemistry and immunology tests. During fiscal year 1978, three committees (or subcommittees) reviewed the diverse applications submitted. Balance and expertise in each committee's deliberations are assured by members who are active investigators, and nationally and internationally recognized leaders in many of the disciplines relevant to the cancer problem. The disciplinary composition of each committee is matched insofar as possible with the disciplinary composition of the applications it reviews. Committee recommendations are considered by the National Cancer Advisory Board as required by the National Cancer Act.

The Review Committees

(1) The Cancer Special Program Advisory Committee (CSPAC) reviews proposals requesting program project support and construction support for basic science. Review of these complex, multidisciplinary applications constitutes the bulk of the Committee's work. CSPAC has fourteen members with expertise in the basic sciences related to the cause, treatment, and prevention of cancer. Members must understand medical school and university organization, administration of program projects and construction projects, and be sensitive to the effect on the applicant institution caused by initiation, continuation, or termination of a large-scale project. The group advises the NCAB and NCI regarding the merit and probable success of the basic research program projects and related construction projects that come before them.

(2) The Clinical Cancer Program Project and Cancer Center Support Review Committee was established during the year by merging two previously independent committees in compliance with the objective of DHEW to reduce the number of advisory committees. Through two independently functioning subcommittees,

applications are reviewed for program project support concerned with clinical problems in cancer, in one case, and applications for core support of comprehensive, clinical, and specialized research centers in the other. Both subcommittees review construction applications related to their activities. Because of the complexity and volume of the work performed, each of these subcommittees functions independently. Each subcommittee consists of twenty members appointed by the Director of the NCI.

(a) The Cancer Center Support (Core) Review Subcommittee (CCS) provides merit review for requests to fund large cancer centers (core grants) submitted by designated comprehensive cancer centers and by specialized centers as well as applications to fund construction or renovation of related cancer facilities. The subcommittee is also a resource for advice on related cancer research programs, current status of ongoing centers, and identification of areas for future emphasis. Review by CCS helps alert the NCAB to the problems raised by, and the opportunities inherent in, the applications from the Centers in terms of the mission of the NCI .

The responsibilities of the CCS require that the members of the Committee have broad knowledge of the basic sciences that can contribute new information about the cause and prevention of cancer and of the clinical sciences involved in the diagnosis and treatment of cancer. In addition, knowledge of the administration and organization of medical schools, universities, and free-standing cancer research organizations is essential. Sensitivity to institutions' organizational needs is important. Reviewers must be able to recognize those management practices that encourage good research.

(b) The Clinical Cancer Program Project Review Subcommittee (CCP) provides merit review of applications requesting support of clinical program projects and related cancer research programs. It also identifies areas for future emphasis, and makes suggestions for innovative approaches to the cancer problem. The review of large clinical research grant applications requires special expertise in cancer clinical trials; understanding of the special demands of research with human subjects; of hospital and medical school organization; of the administration of program projects; and, most importantly, detailed expert knowledge of the diagnosis and treatment of all types of cancer.

During the year, the Referral Office received and assigned approximately 2,700 applications. The three committees or subcommittees of the Branch reviewed 153 grant applications requesting a total of approximately $491,279,000. Seventy-two percent or 118 applications were recommended for approval with recommended budgets totalling approximately $172,217,000 or 41 percent of the total requested in all the approved applications. The recommended budgets amount to 35 percent of the total request for all applications reviewed. A total of $239,183,000 was disallowed in the approved grants. Although the approval rate of 77 percent is high compared with the rest of NIH, the recommended funding rate of 35 percent is generally in line. It should be noted that programmatic and financial considerations often dictate budget negotiations which further reduce the percentage paid to below the recommended level. The significance of the work of the Branch to the mission of the NCI is suggested by these figures. However, the true significance lies in the expert advice obtained which permits the National Cancer Advisory Board and the Director, NCI, to select for funding that research best suited to fulfill the mission of the NCI.

REVIEW & REFERRAL ACTIVITY: OCTOBER 1, 1977 THROUGH MAY 30, 1978

REVIEW *GROUP	DIRECT COST REQUESTED ALL APPLICATIONS		DIRECT COSTS RECOMMENDED APPROVED APPLICATIONS		DIRECT COST REQUESTED IN APPROVED APPLICATIONS**	AMOUNT RECOMMENDED APPROVED APPLICATIONS	AMOUNT DISALLOWED ON APPROVED APPLICATIONS**	APPROVAL RATE	
	NO.	AMOUNT**	NO.	AMOUNT**				NO.	$AMOUNT
CAK	51	$129,096	41	$ 54,345	$111,974	48%	$ 57,651	83%	43
CCP	44	138,592	36	42,175	122,340	35%	80,165	82%	30
CCS	40	183,512	28	55,412	143,453	39%	88,041	68%	30
SRC	18	40,079	13	20,285	33,611	60%	13,326	72%	51
TOTAL	153	$491,279	118	$172,217	$411,378		$239,183		

Total Direct Costs recommended $172,217,000 (35% of total requested).
Total of requested budgets of disapproved applications $79,001,000 (16%).
Total of requested budgets disapproved plus amounts disallowed on approved applications $319,084,000 (65%).

*CAK=CANCER SPECIAL PROGRAM ADVISORY COMMITTEE
CCP=CLINICAL CANCER PROGRAM PROJECT REVIEW COMMITTEE
CCS=CANCER CENTER SUPPORT GRANT REVIEW SUBCOMMITTEE
SRC=SPECIAL REVIEW COMMITTEE

**In thousands of dollars
All figures are approximate due to rounding.

TUMOR BIOLOGY PROGRAM

Description

The Tumor Biology Program supports biological and biochemical research in the area of cancer biology. The major long-term objectives of the Program are to develop a complete understanding of the biological processes in malignant cells that contribute to loss of growth control and lead to penetration and invasion of surrounding tissues. Research efforts range from descriptive studies of tumor progression and vascularization in animals and humans to the most sophisticated molecular studies of regulatory mechanisms in normal and neoplastic cells. Two of the basic premises of this program are that abnormalities of neoplastic cells will not be understood completely until more is known about normal cell function, and that the identification of unique properties associated with cancer cells ultimately will lead to improved treatment, therapy, and diagnosis of cancer. The basic and cancer-specific information developed in this Program is of fundamental importance to nearly every other program area of the National Cancer Institute.

Accomplishments

Both developmental biology and oncology attempt to explain what factors contribute to the orderly or disorderly control of cell migration, cell communication, and cell interaction. There is increasing evidence that nearly all of these processes become aberrant during neoplasia. Below are highlights of results obtained in the Tumor Biology Program over the last year.

Dr. Werner R. Loewenstein and his group at the University of Miami have demonstrated a correlation between the ability of cells to communicate and growth control. When communication-competent human fibroblasts were hybridized with communication-incompetent tumorigenic mouse cells, the hybrid cells were able to communicate and were subject to normal growth controls. However, as segregants emerged due to loss of human chromosomes, every segregant that became communication-incompetent also was no longer subject to normal growth control. In addition, only the communication-competent cells retained the ability to form gap junctions, which are specialized membrane structures of two apposing cells believed to be responsible for ionic-coupling and metabolic coupling (Azarria and Loewenstein, 1977; Larsen *et al* 1977). These results suggest that in some cases the inability of cells to communicate may be responsible for uncontrolled growth. At a minimum, these results indicate that the chromosome containing the information for communication competence also contains other genes responsible for maintaining control over cell multiplication.

George Lipkin has isolated a diffusible factor prepared from the culture medium of contact-inhibited hamster melanocytes. Density-dependent regulation or "contact-inhibition" in vitro is a property of normal cells, the loss of which is correlated with in vivo tumorigenicity. The melanocyte contact inhibitory factor (MCIF) restores the capacity for contact inhibition of growth to malignant melanocytes of man, mouse, and hamster. In addition, MCIF inhibits growth in vitro of a broad spectrum of malignant cell types of ectodermal, mesodermal, and endodermal origin. A factor also has been obtained from a line of human epidermal cells that is electrophoretically and functionally identical with MCIF. It is not known whether these factors affect cell communication, deformability, or association, but they may represent a general class of cell-surface active agents that control neoplastic growth (Lipkin et al, 1978).

Density-dependent regulation of growth may be due to diffusible factors or to direct cell-cell contact. The two-dimensional in vitro cell culture systems now used may be too artificial to sort out which of these factors contributes most to growth control. A system has been developed which cultures cells as aggregates of 1000 to 5000 cells in agitated liquid medium. This three-dimensional system uses no artificial surfaces and already has yielded results that differ from conventional two-dimensional systems. Its further use should yield more realistic information about cell-cell interactions and growth control. (Carrino and Gershman, 1977).

Collagen is a basic component of the intracellular matrix that fills the spaces between apposing cells. A cell attachment variant of a Chinese Hamster Ovary Cell Line has been selected for its altered ability to attach to collagen. It has been suggested that this result provides additional support for the role of collagen in cell adhesion. The isolation of cell attachment variants should be of considerable aid in the biochemical analysis of cell-surface receptors involved in intercellular adhesion (Klebe et al, 1977).

Circumstantial evidence continues to implicate changes in cell- surface carbohydrates as important factors contributing to malignant transformation. The glycopeptides of a rat liver epithelial cell line were compared to their temperature-sensitive transformed counterparts. The results clearly established that specific alterations in the cell-surface glycoproteins accompanied expression of the transformed phenotype (Pietropaolo, 1977). Studies with mouse melanoma variants of low and high metastatic potential indicate that the total lipid-bound and protein-bound sialic acids are reduced in the high variant. These results tend to support a role for sialic acid in implantation, tumorigenicity, and tumor cell immunogenicity (Yogeeswaran et al, 1978). The organ distribution, arrest, and survival of these same variants were tested in a variety of normal and immunosuppressed mice. While host properties affected arrest and survival, they did not diminish or abolish the biological differences between the high and low metastatic cell lines (Fidler and Nicolson, 1978). These results suggest that certain properties of the tumor alone, possibly cell-surface properties, contribute to the outcome of metastasis.

One theory of tumor invasion is that the cancer cell secretes proteases that facilitate the breakdown of intracellular matrices during its migration. Primary tumors of a rabbit VS-2 carcinoma release both a tumor specific collagenase and a neutral protease (Dabbous et al, 1977). The possibility that two enzyme activities may function synergistically to facilitate tumor invasion is worthy of further investigation.

Retinoids may have some importance in the control of epithelial cancer. Because the biological activity of retinoic acid parallels that of Vitamin A (except that retinoic acid has no role in vision or reproduction), there is at least the potential for nutritionally controlling the progression of some kinds of tumors. It is known that retinoic acid binding protein (RABP) is essential for the mediation of retinoic acid action. Drs. Sani and Titus have demonstrated that RABP is present in a number of experimental tumors and tissues with metastatic foci. They suggest that the presence of this binding protein may be used as a positive biochemical parameter for retinoic acid therapy (Sani and Titus, 1977).

It has been known for some time that tRNA melthyltransferases are aberrantly hyperactive in every malignant tumor examined and that there are a few isoaccepting tRNA's that are tumor specific. The phenylalanine isoaccepting tRNA's specific to Novikoff hepatoma and Ehrlich ascites cells contain two supernumerary methylated bases, one of which is absent from normal liver tissues. This is the first unequivocal evidence that there is an aberrant modification of a tumor-specific tRNA (Kuchino and Borek, 1978). Now it is important to determine what functional changes accompany such aberrant modifications and whether these functional changes contribute to tumorigenicity.

Because alterations of surface membranes appear to be critical during the development of neoplasia, it is important to study potential ways of altering the composition of tumor cell membranes. One way of approaching this problem is to assume that rapidly developing cells will preferentially use substrates that are provided nutritionally in a ready-to-use form. By controlling the fatty acids in the diet, for example, it is conceivable that tumor-membrane function can be altered. Recent basic information supporting this hypothesis is that the affinity of membrane proteins for liposomes is either increased or decreased depending on the protein and phospholipid composition of the liposomes (Eytan and Racker, 1977). Also, the amino acid transport functions of Ehrlich ascites tumors change when mice are fed different types of fatty acids in the diet. (Dabbous et al, 1977). Utilization of fatty acids by human leukemic blast cells and murine L1210 leukemic cells can be controlled because these cells directly utilize fatty acids in the extracellular environment (Burns et al, 1977a; Burns et al 1977b). It may be possible, then, to alter the fatty acid composition of membrane phospholipids, and presumably membrane function, by changing the proportion of various free fatty acids supplied in the diet. Whether these alterations can help to bring about reversal of tumorigenic properties is a question that remains unanswered.

A platelet aggregating principle has been observed in two mouse ascites tumors and their cell-free supernatants. This factor is present in numerous other tumor cell lines and apparently is a protein. Because it is not present in five varieties of nonneoplastic cells, such an activity could be an indicator of malignant transformation or malignant progression (Gasic _et al_, 1977). It could also be an important factor contributing to tumor invasiveness, since the activity is highest in mouse tumors that are the most active in their metastatic potential.

There is a consistent occurrence of nonrandom chromosomal changes in human malignancies. It has been hypothesized, and in many cases documented, that certain chromosome instability syndromes are accompanied by a high risk of contracting cancer (Hecht and McCaw, 1977). Many hematologic malignancies are characterized by specific chromosomal rearrangements and gene deletions (Rowley, 1977). Studying the chromosomes of malignancies may reveal patterns that can help determine which individuals are at highest risk as well as indicate some of the reasons why malignant cells might have a proliferative advantage over normal cells.

Emphases and Projections

The Tumor Biology Program will continue to emphasize and encourage research in the following areas:

(a) Characterization of cell surface structural and compositional changes specific to tumor cells, especially alterations of glycoproteins and glycolipids.

(b) Descriptive and molecular characterization of biological processes that potentially contribute to invasiveness and metastasis (e.g., cell migration, cell-cell communication, and cell-cell adherences).

(c) Establishment of model culture and animal systems that permit combined biological and molecular analyses of tumor progression (e.g., B16 melanoma high and low metastasizing variants).

(d) Characterization of the specific growth factor and nutritional requirements of tumor cells _in vitro_ and _in vivo_.

(e) Characterization and definition of the molecular controls associated with the cell growth cycle.

(f) Expanded research efforts in the area of tumor vascularization, especially the characterization and mechanism of the tumor angiogenesis factor (TAF).

(g) Expanded research efforts to define metabolic patterns characteristic of cancer cells.

(h) Expanded research efforts to define control mechanisms involved in gene expression.

Other Program Activities

In the past year the Tumor Biology Program actively participated in the organization of a conference focused on mutants of the cell growth cycle. In addition, advice and consultation have been provided to two other potential conferences focusing on cancer cell membranes, and differentiation and neoplasia.

FISCAL YEAR 1978

TUMOR BIOLOGY PROGRAM

SUMMARY BY SUB-CATEGORY
(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
CELL SURFACE	54	$ 3,858	28	$ 1,974	82	$ 5,832
ENZYMES	26	2,106	11	642	37	2,748
PEPTIDE HORMONES	9	677	4	312	13	989
STEROIDS	11	972	5	436	16	1,408
MEMBRANEOUS ORGANELLES	14	1,642	2	133	16	1,775
RIBOSOMES AND POLYRIBOSOMES	10	998	2	287	12	1,285
M-RNA	14	929	5	526	19	1,455
T-RNA	6	411	1	66	7	477
DNA	18	1,438	9	792	27	2,230
GROWTH FACTORS	10	817	11	907	21	1,724
NUCLEUS	22	1,595	4	309	26	1,904
CONTRACTILE ELEMENTS	4	247	2	166	6	413
DEVELOPMENT AND DIFFERENTIATION	25	2,047	23	1,690	48	3,737
CELL GROWTH, CELL DIVISION	15	1,197	11	904	26	2,101
SOMATIC CELL GENETICS	10	1,015	2	147	12	1,162
INHERITANCE OF NEOPLASMS	3	168	0	0	3	168
PLASMIDS, VIRUSES	3	99	1	127	4	226
IN VIVO AND IN VITRO TUMOR LINES	1	367	2	88	3	455
MISCELLANEOUS	4	299	2	150	6	449
PROGRAM PROJECTS	9	4,355	4	2,224	13	6,579
CONFERENCE	1	69	3	25	4	94
YOUNG INVESTIGATORS	0	0	8	233	8	233
TOTAL	269	$25,306	140	$12,138	409	$37,444

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IMMUNOLOGY PROGRAM

Description:

The Immunology Program of the National Cancer Institute is focused on the development of effective immunologic approaches to cancer prevention, diagnosis, and treatment. Because these approaches are dependent on an understanding of immune mechanisms, much of the program emphasis is on basic immunology.

Both basic and clinical research are supported in the following areas: identification, isolation, and characterization of cell surface antigens; immunogenetics; immunodiagnostic tests for cancer; antibody structure, synthesis, and function; humoral factors involved in immunologic reactions; cellular immunology; immune status; immunoprophylaxis against cancer; *in vitro*, animal, and clinical studies of cancer immunotherapy and immunologic aspects of bone marrow transplantation in man and animals.

The Immunology Program currently supports 367 grants in the traditional program and 19 program projects with a total cost of $37 million.

Accomplishments:

The Immunology Program supports research studies in (a) cancer cause and prevention, (b) detection and diagnosis, (c) therapy, and (d) biology.

(a) Cause and Prevention:

The concept that the surface of a tumor cell differs qualitatively or quantitatively from its normal counterpart has focused attention on the ability of the immune system to recognize and react with a developing tumor.

One suggestion is that transformation of a cell and its subsequent recognition and destruction by the immune system is a common event. To date, the main evidence cited in support for such an immune surveillance mechanism is the higher incidence of certain types of cancer in immunologically deficient animals and man, but the concept is still under active debate.

One of the most active areas of research relating to immune surveillance today, is the role played by natural killer (NK) cells. Characterization of NK cell activity has been difficult because a marker has not yet been found which uniquely distinguishes these from other cells of the immune system and which can be then utilized in cell separation procedures. Recent work has demonstrated a relationship between cells with NK activity and marrow-dependent cells which are responsible for resistance of F. hybrids to parental hemopoietic grafts (Kiessling, et al., 1977). Whether these are activities of identical or related cell populations is unknown at present.

Prehn and his collaborators have been instrumental in gathering evidence which suggests that recognition of a tumor by the immune system can stimulate tumor growth rather than retard it (Prehn, 1977). While this hypothesis is not mutually exclusive with the idea of immune surveillance, it does underline the complex and dynamic nature of the relationship between tumor development and immune function.

It may well be that the oncogenic agent is important in determining the outcome between immune response and tumor (Klein and Klein, 1977). For example, several oncornaviruses have been demonstrated to be immunosuppressive. Also, cells transformed by such viruses maintain antigens on their surface which are highly immunogenic, and this would tend to increase the likelihood of immune recognition. While tumors induced with high concentrations of chemical carcinogens also tend to be very antigenic, spontaneous tumors have been repeatedly shown to be poorly immunogenic. This has led some investigators to suggest that the continuous interplay of the growing tumor with the immune system places a selective pressure on the tumor to progress to a type poorly recognized by immune effector mechanisms. In support of this concept, several laboratories have been able to clone tumors into subpopulations which can differ in their immunogenicity, growth potential, and ability to form metastases (Bulloch, et al., 1977).

Even from this brief discussion, it is apparent that this general area is one of sufficient interest and complexity to ensure continued activity.

(b) Detection and Diagnosis:

The search for antigenic markers which can be used in the specific and accurate detection and diagnosis of cancer is an important area. Progress here is highly dependent on our basic understanding of cell surface structure with perhaps particular need for more information on the changes in surface structure which occur during the developmental process.

For example, Cooper and his associates in Alabama have applied concepts and techniques developed in model systems using avian and murine lymphocytes to the classification of human leukemias and lymphomas (Gathings, et al., 1977). Similar efforts are ongoing in a number of laboratories (Minowada, et al., 1977) and these studies may have important relevance in disease classification and prognosis.

Carcinoembryonic antigen (CEA) has a history that is representative of the problems presented by several antigens whose presence was first thought to be indicative of cancer. As information has accumulated concerning this marker, it has become evident that its distribution and presence in a variety of tissues and in a variety of diseases limit its usefulness as a specific indicator for gastrointestinal malignancy. At present, there is some evidence that a finding of several sequential elevated measurements of CEA serum titers may be useful in indicating recurrent cancer (Lowenstein and Zamcheck, 1977). Alphafetoprotein is a second marker whose use is limited because it is found associated with diseases other than cancer, but which has been applied to the diagnosis of hepatocarcinomas and teratocarcinomas (Egan, et al., 1977).

An avenue of approach which holds considerable promise in predicting cancer prognosis is the assessment of circulating antibodies specific for their own tumors in patients with malignancies. Old and his colleagues at Sloan Kettering Institute have performed an exacting analysis of serum reactivity against autologous melanoma cells. Three categories of melanoma cell surface antigens were demonstrated: (a) unique melanoma antigens restricted to autologous tumor cells; (b) shared antigens also found on some allogeneic cells; and (c) antigens not restricted to melanoma cells. Interestingly, the pattern of a patient's serum reactivity can change from one category to another during the time course of the disease (Shiku, et al., 1977). Diagnostic usefulness of reactivity to antigens in the third category may be limited. For example, Ferrone and co-workers at Scripps have screened a large panel of sera for reactivity against cultured melanoma cells and have found reactivity in samples from many patients with cancers other than melanoma. (Ferrone and Pellegrino, 1977).

There continues to be interest in the association of blood group precursor substances and compounds of similar structure with various forms of cancer. For example, Springer has demonstrated that human blood group MN precursors (T and Tn) which are masked in healthy tissues are exposed and reactive in patients with breast cancer. These T-specific antigens are capable of eliciting both humoral and cell-mediated immune responses in patients with this disease (Springer, et al., 1977). Confirmation of this important finding has now come from two additional laboratories. A similar approach is being used by Hakomori and by Levine in studying the association of Forsman-like antigens with gastric and colonic cancer (Hakomori, et al., 1977).

(c) Therapy:

The direct application of immunology to the therapy of cancer has proven a difficult task. The gaps in our basic understanding of immunological mechanisms and processes have severely limited present ability to develop effective therapeutic protocols.

It was originally thought that all cancer patients with moderately advanced disease were anergic. More thorough examination has shown that this is often not the case and while some cancer patients show partial immune deficits, others are normal for a wide spectrum of immune functions. Still, there are numerous efforts to boost immunity in some non-antigen specific way as a form of immunotherapy. The use of bacterial products has been widely used, and one of the more promising efforts is that of McKneally and his co-workers (McKneally and Maver, 1977). Their results with intrapleural injection of BCG in the immediate postoperative period in cases of Stage 1 localized lung cancer indicate a significantly lower incidence of tumor recurrence in those patients receiving immunotherapy as compared to the control group. Modest success with BCG immunotherapy has also been achieved by several groups studying malignant melanoma. In the laboratories of Morton, a method of optimizing BCG therapy has been developed which involves measurement of the host serum antibody titer to the BCG organism (Wile, et al., 1977).

Specific immunotherapy has also been difficult to approach because of problems in identifying and characterizing tumor-associated antigens and then using these to generate either specific antibody or specific cytotoxic cells. As our immunochemical sophistication continues to develop by the use of techniques such as affinity chromatography, we can expect greater success in antigen characterization (Bystryn, 1977). One interesting solution to the problem of finding tumor-specific antigens is the use of antigen receptors on the cell surfaces of lymphoid tumors as the target molecules. This is a direct extension of basic research on idiotypy. A second area which is beginning to develop involves the production of monoclonal antibodies against tumor-associated antigens. Such antibodies can be produced by selective cloning or by use of somatic cell hybridomas. For example, Levy has reported the production of a monoclonal antibody against human leukemia cells (Levy and Dilley, 1977). Such antibody might be used in therapy alone or as a mechanism for improving drug delivery to the tumor.

(d) Biology:

It is within this thrust that the Immunology Program supports a variety of studies in basic immunology. These provide the groundwork for the more definitive application of immunology to the prevention, diagnosis, and therapy of cancer.

The ability of antibody responses to discriminate between a large number of antigenic specificities has stimulated considerable research on the origin and nature of the genes which control immunoglobulin structure, the synthesis of the protein, and the structure of the final product. Hybridization of complementary DNA probes with host genetic material has shown that a small number of copies of any C or V region gene exist, thus providing support for the somatic mutation method of generating structural diversity. A nucleotide "spacer" sequence in messenger RNA between the sequences defining the constant and variable regions of the immunoglobulin molecule has been found (Wall, et al., 1977; Bedard and Huang, 1977). The role played by this spacer is undefined, but the presence of such a sequence has now also been found in mRNA's for other mammalian proteins. Both the carboxy and amino terminal ends of the initial immunoglobulin polypeptides appear to contain extra amino acids not found in the final secreted product (Burstein and Schechter, 1977). The ends of the mRNA molecule contain analogous extra sequences (Cory, et al., 1977). It is yet to be discovered whether these extra sequences of amino acids and nucleotides play a role in the assembly of the molecule, in membrane attachment during synthesis and secretion, or some other function.

Structural and genetic studies on the major histocompatibility complex of man (HLA) and mouse (H-2) continue to attract the attention of many workers (Silver, et al., 1977; Freed and Nathenson, 1977; Schreffler, et al., 1977). These complexes not only contain the genetic code for antigens important in transplantation rejection but also include genes (in the I region) which are significant to cell-cell collaboration in immune responses and in determining responsiveness to particular antigens.

Both H-2 and Ia antigens have similar polypeptide and carbohydrate structures, and this has focused attention on their possible common ancestory. The reported existence of highly variable amino acid sequences in these molecules raises questions on the relationships between the genes coding for immunoglobulin molecules and these antigens.

In addition to controlling T cell responsiveness, the major histocompatibility complex also plays a significant role in defining the antigenic structure of the cell surface. In an attempt to explain the requirement for target and killer cells to share a restricted histocompatibility type, Bevan and colleagues (Matzinger and Bevan, 1977) have postulated that H-2 antigens are able to associate physically with any of a large number of other cell surface antigens to yield a unique complex antigen.

A significant advance towards resolution of the many questions concerning the nature of the antigen receptor on thymus-derived lymphocytes has been the ability to maintain in vitro lines of T cells with specificity against alloantigens (Dennert and Raschke, 1977; Gillis and Smith, 1977). Such lines can be produced by repeated stimulation in one-way mixed lymphocyte cultures and provide a homogeneous source of material useful in serological and biochemical analysis of the antigen receptor.

The surface phenotypes of murine lymphocytes as exemplified by study of the antigens of the Ly series, continue to be useful in exploring the functions and interactions of the immune system. For example, it has been demonstrated that Ly $2,3^+$ killer cells require Ly 1^+ helper cells as well as recruitment from an Ly $1,2,3^+$ precursor population for maximal cytotoxicity against a mammary tumor (Stutman, et al., 1977). An analogous phenotype on B cells (Lyb_3) has been shown to be involved in antigen-dependent activation of these cells (Huber, et al., 1977).

Considerable work has shown that it is difficult to correlate immune parameters as measured in serum or with peripheral blood leucocytes with the disease status of a tumor-bearing host. There are now techniques available for isolating leucocytes directly from solid tumors and this may enable one to make more exacting correlations between immune response and tumor growth or rejection (Hansen, et al., 1977).

The role played by idiotypic determinants in defining the interaction between an immune response and tumor development has been studied by Lynch and co-workers (Rohrer, et al., 1977). Using a murine myeloma tumor as a model system, they were able to show that both antigen (in this case myeloma protein) and anti-idiotypic antibody can cause repetitive cycles of differentiation during growth of the tumor. As described earlier, such studies are suggestive of new approaches in therapy.

Emphases and Projections

(a) Production of Specific Antibody by Somatic Cell Hybrids: A technology is rapidly developing for the in vitro production of large amounts of antibody of a chosen specificity. Such antibody could likely be produced against tumor antigens such as idiotypic determinants on the surface of B cell lymphomas. Such antibody could be used to monitor tumor load and thus produce information useful in diagnosis. In addition, specific passive immunotherapy might be possible. Additional funding could be used to stimulate the development of this technology. Increasing hybridization efficiency, rapid screening methods for detecting the most useful hybrids, and enhancement of secretion rates of specific antibody are all areas which could be stressed.

(b) Recognition of Cell Surface Antigens: Immune recognition is a first step in all immune responses. There is a need for more information on the way(s) in which the immune system recognizes determinants on the surface of tumor cells. Added emphasis could be given to the structural basis of the relationships between histocompatibility antigens and viral-determined cell surface antigens and between histocompatibility antigens and haptenic determinants. Modulation of the recognition process, for example increasing the immunogenicity of tumors by coupling haptens to their surface, may be possible, resulting in increased therapeutic possibilities. In addition, knowledge of what is recognized provides information on the specificity of the receptors responsible for recognition. The mechanics of antigen recognition by T cells is one of the most fundamental problems in basic immunology.

(c) Immune Reactions in Carcinogenesis: The carcinogenic process appears to involve a complex series of events, and increased emphasis could be given to the participation of the immune response in this sequence. For example, the operation of an effective surveillance mechanism against tumor development is debatable and requires resolution. Chronic U.V. exposure has been reported to suppress the immune response and induce tumors, and this relationship should be clarified. An immune response to chemical carcinogens might affect their in vitro distribution and thus contribute to cancer induction, but few studies have examined this possibility to date. In animal systems, evidence suggests that an immune response can play a role in activating the carcinogenic potential of oncornaviruses. Clearly, an interface between immunology and carcinogenesis is rapidly developing which will require enhanced support.

(d) Developmental Aspects of the Lymphoid System and Tumor Classification: A variety of physical, biochemical, and immunological properties can be used to define the developmental lineage of a given subclass of lymphoid cells. An increased emphasis can now be given in applying such classification techniques to lymphoid neoplasms. Detection of disease and accurate diagnosis can be facilitated by study of such parameters as the cell surface antigenic characteristics of a tumor cell population, its density, and the enzymes by which it synthesizes and repairs its nucleic acid. It is likely that such classification can be further used to predict more accurately the prognosis of a given tumor to various therapeutic modalities.

Other Program Activities:

In order to encourage the rapid dissemination of research findings, the Immunology Program also supports meetings and conferences. Among those supported in whole or in part during this fiscal year are:

"Escape from Immune Surveillance: An Interpretive Survey of the Interface Between Immune Mechanisms and Disease" - Brook Lodge, Augusta, Michigan - December 1977.

"Symposium on Antigen Recognition (Self/Non-Self Discrimination)" - Toronto, Canada - December 1977.

"Workshop on *In Vitro* Induction and Measurement of Antibody Synthesis in Man" Utrecht, The Netherlands - March 1978.

"Genetic, Molecular, and Functional Aspects of Specific Immune Response Genes and Their Products" - Annapolis, Maryland - May 1978.

"H-2 Mutations - A New Tool in Immunology" - Woods Hole, Massachusetts - May 1978.

"VIIIth International Congress of the Reticuloendothelial Society" - Jerusalem, Israel - June 1978.

"Gordon Conference on Immunochemistry and Immunobiology" - Andover, New Hampshire - July-August 1978.

"Conference on Complex Carbohydrates in Biological Recognition" - Bethesda, Maryland - July 1978.

"The Seventh International Congress of the Transplantation Society" - Rome, Italy - September 1978.

"Workshop on Genetic Control of Autoimmune Disease" - Bloomfield Hills, Michigan - June 1978.

"Third Conference on Mononuclear Phagocytes" - Leiden, The Netherlands - September 1978.

FISCAL YEAR 1978

IMMUNOLOGY PROGRAM

SUMMARY BY SUB-CATEGORY
(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
ANTIBODY STRUCTURE, SYNTHESIS AND FUNCTION	18	$ 1,601	12	$ 888	30	$ 2,489
IDENTIFICATION OF CELL SURFACE ANTIGENS	52	3,858	18	1,283	70	5,141
CELLULAR IMMUNOLOGY	70	5,209	51	3,856	121	9,065
DIAGNOSTIC TESTS	1	61	0	0	1	61
HUMORAL FACTORS OTHER THAN ANTIBODY	12	825	3	231	15	1,056
IMMUNODIAGNOSTIC TESTS FOR CANCER	4	371	2	231	6	602
IMMUNOGENETICS	30	2,632	25	1,886	55	4,518
IMMUNOPROPHYLAXIS	1	53	0	0	1	53
IMMUNE STATUS	24	2,305	13	946	37	3,251
IMMUNOTHERAPY ANIMAL MODELS IN VITRO STUDIES	22	1,650	8	586	30	2,236
CLINICAL IMMUNOTHERAPY	5	341	3	345	8	686
MECHANISMS FOR IMMUNOTHERAPY	6	520	3	178	9	698
PROGRAM PROJECTS	12	9,777	12	6,028	24	15,805
YOUNG INVESTIGATOR AWARDS	0	0	1	33	1	33
TOTAL	257	$29,203	151	$16,491	408	$45,694

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Description

The Carcinogenesis Program seeks to achieve a more effective prevention of human cancer, caused or promoted by chemical and physical agents, acting separately or together, or in combinations of either or both of these classes of carcinogens. Studies supported under this Program bear upon the fields of both environmental and occupational carcinogenesis, the role of diet and nutrition in the carcinogenesis process, and the inhibition of carcinogenesis by dietary, hormonal, and analogous means, as well as research on the reactivity of chemical and physical carcinogens and their mechanisms of action.

The Program includes two complementary categories of research: Chemical and Physical Carcinogenesis and Cancer Biochemistry. The kinds of research supported under the first of these categories are: (a) molecular structure-carcinogenicity relationships, (b) synthesis of chemical carcinogens and their metabolites, (c) development of analytical procedures applicable to body fluids, tissues, and environmental specimens, (d) elucidation of biochemical and ultrastructural changes in physiological macromolecules and processes produced by chemical and physical carcinogens, with particular reference to changes in DNA, RNA, and proteins, (e) development of procedures for the screening of substances for possible carcinogenicity, as well as the development of biological models and bioassay systems for use in analogous studies, (f) metabolism/activation of chemical carcinogens, identification of proximate and ultimate carcinogenic species, carcinogen-mutagen relationships, (g) the further definition of enzymatic and nonenzymatic processes characteristically associated with activation and inactivation of chemical carcinogens, (h) the phenomenon of promotion in carcinogens and the identification of promoters present in the environment, (i) factors which modify the carcinogenesis process, such as age, sex, species, cocarcinogens, inhibitors and the influence of drugs, food additives, diet, and nutrition, and (j) significance of DNA repair in carcinogenesis. In the Cancer Biochemistry category, the focus is on those biochemical aspects of cancer cells and cancerous hosts significantly associated with the carcinogenesis process. This category is devoted to studies intended to define and quantitate phenomena which have a significant bearing upon the carcinogenesis process, both in vivo and in vitro. Within this category the emphasis is on: (a) endocrine-related biochemistry; particularly studies on hormone sensitive tumors and the extent to which hormones affect the carcinogenesis process, (b) enzyme, lipid, and other biochemical changes associated with the cellular progression to neoplasm, (c) development of methods for the detection of preclinical cancer, and (d) effects of carcinogens, cocarcinogens, and promotions on cell membranes.

Research Accomplishments

Active folic acid degradation with formation of pterin-6-aldehyde, a previously undescribed characteristic of cancer cells in vitro, has been detected in several human, rat, and mouse malignant cell cultures but was undetectable in cultures of normal adult, embryonic, and amniotic cells (Halpern et al., 1977). This finding prompted a comparison of patients with and without cancer to determine whether active folate degradation in vivo is also associated with malignancy. Twenty-nine patients whose diagnoses were not revealed until later were tested for the presence of pterin-6-aldehyde in their urines. The compound was present at about 300 nmol/ml or greater only in those 13 patients subsequently diagnosed as having cancer. Total tumor resection resulted in disappearance of the pterin-6-aldehyde from the urine. The advantage to cancer cells of this particular metabolic pathway is not at all obvious and is under investigation. More patients must be studied and followed for a longer period of time to ascertain the diagnostic and prognostic significance of these findings.

Another biochemical abnormality of potential use in cancer diagnosis or screening has been detected during studies of aryl hydrocarbon hydroxylase (AHH), the enzyme system which activates a number of chemical carcinogens. Although a positive correlation has been reported between high AHH inducibility of phytohemagglutinin-stimulated human lymphocytes and susceptibility to bronchogenic carcinoma, the actual relationship appears to be more complex than this observation would indicate. In some cells or tissues at least, AHH inducibility may not be an appropriate indicator of their hydrocarbon-metabolizing capacity. In low-passage hamster embryo cells, for example, the basal level of AHH activity was high but inducibility by benz(a)anthracene(BA) was low; in R72/3 rat liver cells, basal activity was low and inducibility was high (Diamond and Baird, 1977). The metabolism of benz(a)pyrene was similar in cultures of BA-induced R72/3 cells and uninduced hamster embryo cells, showing that absolute levels of induced AHH are a measure of the hydrocarbon-metabolizing capacity of the cells, while the absolute levels of uninduced AHH are a measure of the initial metabolizing activity after exposure to the hydrocarbon. Inducibility need not correspond to the cells' maximum hydrocarbon-metabolizing capacity.

AHH activity has been compared in pulmonary alveolar macrophages (PAM) and peripheral blood lymphocytes from 47 patients with primary lung cancer and 56 patients bronchoscoped for other indications (McLemore _et_ _al_., 1977). In lung cancer patients, comparable levels of AHH activity were usually not expressed in both types of cells examined. This series of patients was almost equally distributed into those with moderate to high AHH activity in lymphocytes but whose PAM activity was low, and those with low lymphocyte and high PAM activity. In noncancer patients, on the other hand, there was a positive correlation between AHH activity in PAM and a highly augmented induction of AHH over baseline levels in lymphocytes. If AHH abnormalities in the cancer patients are found to be present before the tumor is clinically obvious, a comparison of lymphocyte and PAM enzyme levels might be of value in the early detection of carcinoma of the lung.

When basal and induced levels of AHH in cultured lymphocytes were expressed as augmented induction in this study, the values for cells from smokers without cancer were significantly less than those for cells from nonsmokers without cancer. This indicated that cigarette smoking affects not only the free cells in the lungs of smokers but also cells that circulate in the peripheral blood. Nonsmokers with lung cancer had lymphocyte basal AHH levels and augmented induction values that resembled those of smokers. All but one of the 11 patients, with lung cancer who were classified as nonsmokers had formerly smoked, although an average of more than 20 years had passed since smoking had been discontinued. Such an interval is consistent with the initiation-promotion theory of carcinogenesis.

Tumor promoters, have been the subject of several recent studies. The phorbol diester 12-0-tetradecanoyl-phorbol-13-acetate (TPA), a potent tumor promter in mice, was shown to block induction of DNA synthesis in lymphocytes undergoing the mixed lymphocyte response to foreign histocompatibility antigens (Mastro and Mueller, 1978). The inhibition occurred at some early step leading to cell replication; ongoing DNA synthesis was not significantly affected. TPA also produced a transient inhibition of DNA synthesis in mouse embryo cells pretreated with 3-methyl-cholanthrene (3-MC) (Peterson et al., 1977). The level of 3-MC used did not affect the growth or thymidine incorporation of the cells. Results similar to those obtained with TPA were also seen with other phorbol esters exhibiting tumor-promoting activity but not with phorbol itself, which is not a tumor promoter. This suggests that temporary inhibition of DNA synthesis is associated with the process of promotion.

Addition of TPA to mouse erytholeukemia cells in culture inhibited both spontaneous (Yamasaki et al., 1977; Rovera et al., 1977) differentiation and differentiation induced (Yamasaki et al., 1977) by hexamethylene bisacetamide (HMBA), dimethy sulfoxide, or butyric acid. TPA inhibited HMBA-induced differentiation only if added prior to the time of commitment to differentiation. Preliminary evidence has been obtained that TPA also inhibits differentiation of mouse adipocytes and teratocarcinoma cells in culture (Rovera et al., 1977). Phorbol derivatives that are inactive as tumor promoters did not arrest cell differentiation.

These findings suggest a possible mechanism for tumor promotion; TPA may block the steps involved in terminal differentiation and thus allow unrestrained cell proliferation. Moreover, the fact that TPA can inhibit differentiation in diverse cell types suggests that there may be common mechanisms which trigger commitment of cells programmed for a variety of patterns of cellular differentiation (Yamasaki et al., 1977). If further study should continue to show a direct correlation between known tumor-promoting activity *in vivo* and inhibition of differentiation of Friend eythroleukemia cells, the system could be used to screen suspected tumor promoters.

One of the earliest and most consistent effects of TPA is induction of ornithine decarboxylase. In a recent study of this phenomenon, TPA induced the enzyme in both normal and chemically transformed hamster embryo fibroblasts (O'Brien and Diamond, 1977); induction was greater in the transformed cells. Ornithine decarboxylase was also induced in these cells by adding fresh medium to the cultures. When both fresh medium and TPA were added, the effect of the medium was markedly potentiated in transformed, but not in normal, cells. Transformed and normal hamster embryo fibroblasts thus apparently differ in their regulation of ornithine decarboxylase. The significance of such an alteration for the growth of these cells or their expression of the malignant phenotype is unknown; however, activities of both ornithine decarboxylase and its biosnythetic product, putrescine, are elevated in neoplastic tissues. Moreover, among a number of vitamin A analogs tested, the ability to inhibit TPA-induced ornithine decarboxylase activity correlated with the ability to inhibit skin tumor promotion (Verma and Boutwell, 1977).

Benzyl thiocyanate is among several compounds found to inhibit the neoplastic effects of chemical carcinogens. Benzyl thiocyanate and the corresponding isothiocyanate and phenethyl isothiocyanate occur in cruciferous plants. The latter two compounds and a related synthetic chemical, phenylisothiocyanate, inhibited 7,12-dimethylbenz(a)anthracene-induced mammary tumor formation in rats when administered before the carcinogen (Wattenberg, 1977).

Dietary antioxidants are known to reduce the number and severity of ultraviolet light-induced squamous cell skin tumors in mice. Since UV light can also transform cells in culture, the effect of antioxidents on UV-irradiated cells in culture was examined (Chan and Black, 1977). Ascorbic acid, DL-α-tocopherol, butylated hydroxytoluene, and reduced glutathione all reversed UV light-induced cytotoxicity when administered immediately after irradiation of hamster embryo cells, or when administered before irradiation and left in the medium. There is some evidence that, at least in Xeroderma pigmentosum cells, susceptibilities to the cytotoxic and the mutagenic effects of UV light are related. The extreme mutability of these cells, in turn, is believed to be the basis of their abnormal susceptibility to carcinogens.

Patients with Xeroderma pigmentosum (XP) have an inherited defect in DNA repair, although the specific defect is not identical in all patients. To determine whether S-phase DNA synthesis in XP cells is also abnormally affected by UV radiation, XP and normal human cells were exposed to various doses of UV light (Rude and Friedberg, 1977). In unirradiated cells, no differences in S-phase DNA synthetic rates were detected among classical XP, variant XP, and normal human cell strains. Exposure to UV radiation caused a decrease in S-phase DNA synthesis in all three cell strains. In normal cells, recovery was initiated between 3 and 6 hours and reached a maximum value 65-75 percent that of unirradiated controls by 12 hours after irradiation. In the XP variant cells (which have normal excision repair but defective postreplication repair), recovery was consistently initiated approximately 3 hours later and proceeded at a slower rate than in normal cells. Classical XP cells showed no recovery in the rate of S-phase synthesis during the 24-hour postirradiation incubation period. When the UV fluence to the XP cells was reduced so that survival was approximately that of normal irradiated cells, the kinetics and degree of recovery of the DNA synthetic rate were the same in all three cell strains. These results indicate that pyrimidine dimers are effective blocks to DNA synthesis and that there is no inherent defect in S-phase synthesis in either classic or variant XP cells which is independent of a defect in DNA repair capacity.

K-region epoxides and other reactive metabolites and derivatives of carcinogenic hydrocarbons have been tested for their cytotoxic and mutagenic activities in XP cells (Maher et al., 1977). The survival curves for the three XP strains and the normal control bore the same relationships to one another as did the exponential portions of their respective UV survival curves. It can be inferred from these results that the hydrocarbon derivatives tested cause damage to DNA, that such damage is potentially lethal if left unrepaired, and that both UV-induced and hydrocarbon-induced DNA damage are repaired, at least in part, by a common pathway which is defective in XP cells. At the levels tested, the six parent hydrocarbons failed to cause cytotoxicity. For a given dose of an active epoxide, the frequency of mutation to 8-azaguanine resistance was higher in the XP strains than in the normal cells but mutation frequencies were approximately equal in normal and XP cells at equicytotoxic doses of hydrocarbon derivatives. An unexpected finding was that mutations apparently are not induced by benz(a)anthracene-5,6-oxide even though its cytotoxic effect in these strains is very similar to that of dibenz(a)anthracene-5,6-oxide or dimethylbenz(a)anthracene-5,6-oxide. Further experiments are planned to reassess the mutagenic potential of this compound in this system.

If carcinogen-induced DNA damage and its subsequent repair are relevant to carcinogenesis, as available evidence suggests, then modulation of DNA damage and repair may be an appropriate means of regulating carcinogenesis. Diethyldithiocarbamate (DEDTC), a free radical scavenger, was tested for its effects on DNA strand breakage induced by various carcinogens (Abanobi *et al.*, 1977). DEDTC prevented dimethylnitrosamine (DMN)-induced strand breaks in liver DNA and liver cell necrosis in male Wistar rats. DEDTC also inhibited serum clearance of DMN, methylation of liver DNA, and oxidative demethylation of DMN in the *in vitro* hepatic microsomal system prepared from either rats or hamsters. Interference with the metabolism of DMN appeared to be the mechanism by which DEDTC arrested DMN-induced biochemical and biological effects.

A considerable number of sites on nucleic acid molecules can be predicted, on a strictly chemical basis, to be sites of potential alkylation under certain conditions of pH, solvent, or reagent specificity. The nucleic acid alkylating properties of various classes of carcinogens have been reviewed recently (Singer, 1977). Most alkylating agents of low mutagenicity and carcinogenicity react primarily with the ring nitrogens. Carcinogenic N-nitroso compounds react with all ring oxygens as well as with the phosphodiesters and, in the case of RNA, with the 2'-O of ribose. Ethylating agents show even greater affinity toward oxygen, although in absolute terms they are less reactive than the corresponding methylating agents. The agent, O^6-alkyl guanine can cause base mispairing, and there is evidence that it is not excised from cells that develop into tumors but is excised from other cells; O^4-alkyluracil and O^4-alkyl thymine may play a similar role in tumor development since these derivatives cannot pair normally to adenine but instead may tend to base-pair with guanine. While the amount of O^4-ethylation of thymine is relatively low in double-stranded DNA, it is considerable in single-stranded DNA and it is important to consider that replicating DNA contains single-stranded segments.

Several hydrocarbon metabolites which react *in vitro* with nucleic acids have been proposed as being responsible for the carcinogenicity of the parent compounds *in vivo*. However, the products of reactions between these metabolites and nucleic acids are different from those derived from cells of animals treated with the parent compounds. Non-K-region dihydrodiols of 7-methylbenz(a)anthracene were therefore investigated for their transforming and mutagenic abilities in mouse and hamster cells, respectively (Marquardt *et al.*,
977a). In the transformation test, the 3,4-diol was the most active dihydro-
l tested and the 8,9-diol was also more active than 7-methylbenz(a)anthra-
itself; the 1,2-diol showed only slight activity. The K-region dihydrodiol

(the 5,6-diol), which cannot be directly metabolized to a vicinal diol epoxide, was inactive. Similar results were obtained in the mutagenicity tests.

These results support the general hypothesis that non-K-region dihydrodiols are important in the metabolic activation of carcinogenic polycyclic hydrocarbons and, when considered with other results, indicate that 3,4-dihydro-3,4-dihydroxy-7-methylbenz(a)anthracene is most probably involved in the metabolic activation of 7-methylbenz(a)anthracene, presumably following conversion into the related diol-epoxide, 3,4-dihydro-3,4-dihydroxy-7-methylbenz(a)anthracene-1,2-oxide. The preparation and properties of this and related vicinal diol-epoxides are currently under investigation since formation of vicinal diol-epoxides appears to be the general mechanism of activation of carcinogenic polycyclic hydrocarbons.

The carcinogenic hydrocarbons cause immediate changes in gene transcription and can induce chromosome aberrations; consequently, a direct action of these compounds on the genetic material, as occurs with steroid hormones (which they resemble structurally), is suspected. Effects of metabolism on the binding of hydrocarbons to nuclear subfractions was studied in cultured mouse cells (Spelsberg et al., 1977). A high-affinity localization of ^{3}H-3-methylcholanthrene and/or its metabolites to a specific nuclear fraction was observed between 4 and 72 hours of exposure. Benzo(a)pyrene and dibenz(a,h)-anthracene demonstrated a similar marked localization in this same fraction. Maximal levels of combined covalent and noncovalent binding to DNA occurred at 24 hours of exposure, while at 48 and 72 hours, binding was reduced. The chromatin fraction in which binding was localized is that containing rapidly labeled nascent RNA.

The metabolism of 3-methylcholanthrene by rat liver microsomes has been reinvestigated (Stoming et al., 1977). It appears that the metabolism is much more complex than previously reported and that this hydrocarbon gives rise to at least four possible arene oxides. High pressure liquid chromatography, which has superior resolving power compared with the thin layer chromatography used in previous studies, gave a significantly different metabolic profile. The major metabolites included 1- and 2-hydroxy-3-methylcholanthrene. At least 7 new metabolites, as yet unidentified, were detected; they appear to be diol type derivatives.

Metabolic reactions involved in the activation of arylamines and arylamides for urinary bladder carcinogenesis have not been as clearly elucidated as those for liver carcinogenesis. Metabolism of N-hydroxy-2-naphthylamine (N-OH-2-NA) was studied in uridine-5'-diphosphoglucuronic acid-fortified hepatic microsomes from dogs, rats, and humans (Kadlubar et al., 1977). The test compound was rapidly metabolized to a water-soluble product that yielded 98 percent N-hydroxyamine upon treatment with β-glucuronidase. The metabolite was identified as N-(β-1-glucosiduronyl)-N-hydroxy-2-naphthylamine. At pH 5 this N-glucuronide was rapidly hydrolyzed to the N-hydroxy arylamine, which was subsequently converted to reactive derivatives capable of binding covalently to nucleic acids. Similar results were obtained with N-hydroxy-1-naphthylamine, N-hydroxy-4-aminobiphenyl, and the N-hydroxy-derivatives of 2-aminofluorene, 4-aminoazobenzene, and N-acetyl-2-aminofluorene. These results support the concept that arylamine bladder carcinogens are N-oxidized and N-glucuronidated in the liver and that the N-glucuronides are transported to the urinary bladder. In humans and dogs, as compared with rodents, bladder carcinogenesis may be enhanced by the tendency of the former species toward prolonged storage of acidic urine in the bladder, thus facilitating hydrolysis of the N-glucuronides and accumulation of greater concentrations of free n-hydroxy arylamines and their reactive arylnitrenum ions in the urine.

Several lines of experimental and epidemiologic evidence point to the possible involvement of tryptophan in the causation of human bladder cancer. To define this relationship more clearly, a dietary supplement of tryptophan was administered daily for 4-1/2 years to dogs following a single dose of 4-aminobiphenyl (Radomski et al., 1977). The regimen produced a bladder tumor in 1 of 4 dogs. Daily administration of tryptophan for 3 years following 30 days' daily administration of 2-naphthylamine produced bladder tumors in 2 of 4 dogs. No tumors were observed in either experiment in dogs treated with the carcinogen alone at the doses used, nor did dogs receiving tryptophan alone develop bladder tumors. Most dogs receiving tryptophan, however, developed darkly stained mucosa with white areas of focal hyperplasia. Both experiments suggest a role of tryptophan as a cocarcinogen or promoter in the induction of bladder cancer.

It has been suggested that in vivo nitrosation of certain dietary amines and amides could lead to the production of carcinogenic nitrosamines and nitrosamides in human gastric juices (pH 1-4). Relative to this possibility, fish treated with nitrite was subsequently tested for mutagenicity in Salmonella typhimurium (Marquardt et al., 1977b). Formation of mutagens was highest at pH 3 with 5000 ppm nitrite, but significant amounts were also produced with 1000 ppm. Formation of these mutagens in the nitrite-treated fish was prevented by the presence of ascorbic acid. Nitrite treatment (pH3) of hot dogs, pork, beef, barley, and sour milk produced no detectable mutagens.

Projections

Programmatic emphasis centers on: (a) mechanisms of action of chemical and physical carcinogens, (b) the role of diet, nutrition, and food additives in cancer etiology, (c) the further assessment of the role of promoters in environmental carcinogenesis, (d) the use of dietary and endocrine approaches to the inhibition of carcinogenesis, in vivo, (e) the development of in vitro procedures for the identification of chemical carcinogens, and (f) development of tests for the diagnosis of preclinical cancer.

CARCINOGENESIS PROGRAM

SUMMARY BY SUB-CATEGORY
(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
CHEMICAL CARCINOGENESIS	149	$9,439	65	$4,588	214	$14,027
BIOCHEMISTRY OF CANCER AND CANCEROUS HOSTS	40	3,028	36	2,199	76	5,227
PROGRAM PROJECTS	1	1,075	6	3,300	7.	4,375
CONFERENCES	0	0	3	85	3	85
YOUNG INVESTIGATOR AWARDS	0	0	2	67	2	67
TOTAL	190	$13,542	112	$10,239	302	$23,781

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CANCER EPIDEMIOLOGY PROGRAM

Description

Investigator-initiated research funded by the Cancer Epidemiology Program includes biometry, human genetics, biomedical communications, and epidemiology. As in the past, the majority of the grants support analytic epidemiologic investigations. There are roughly one-third as many biometirc studies and one-fourth as many genetic studies as epidemiologic investigations. The number of program project grants under support has diminished to approximately half the level of recent years. Conferences were concerned with cancer comparisons around the Pacific, genetic methods, epidemiology in cancer research centers, and studies carried out by young investigators.

The biometric studies are the most varied, dealing with many topics from cell kinetics through epidemiologic methods to clinical trials and therapy effectiveness. Funding this year resulted in a considerable growth in cancer biometric research.

The genetic studies also cover a broad range from studies of a single site among twins to genealogic studies of cancer experience in isolated populations. Several of these investigations are developing new methods of analysis in the process of studies which are primarily concerned with cancer etiology. Studies of genetic facets of cancer in human groups (families, siblings, or inbred groups) have grown slowly. This seems to result at least in part from the lack of appropriate laboratory markers delineating cancer risk. The relatively advanced age at which cancer becomes manifest and the long human life-span enhance the need for cancer risk markers in genetic studies.

The epidemiologic studies are spread among a variety of approaches. A communicable agent or common exposure is sought with reference to uterine cervical cancer, Hodgkin's disease, and lymphomas. Carcinogenic agents including intrinsic and extrinsic hormones are examined with reference to breast, endometrial, and ovarian cancer risk, while radiologic exposure and mutagenic substances in body fluids, such as breast and colon fluids, are also investigated. New studies concerned with rhabdomyosarcoma and multiple myeloma have begun. Two studies concerned with behavior were also funded in the last year.

Accomplishments

Heavy smoking and drinking remain as classic risk factors for cancer of selected sites. A recent study of oral cancer takes account of smoking, drinking, and the additional factor, poor dentition (Graham, 1977). Each of these conditions was shown to increase the risk of cancer. However, the risk for men with all three traits was found to be 7.7 times that of men with none. This is greater than the sum of the increased risk from each factor acting independently.

Another site for which smoking increases risk is lung cancer. Earlier reports of arylhydrocarbon hydroxylase inducibility studies in relatives of lung cancer patients created the hope that persons at high risk of lung cancer could be identified on the basis of genetic susceptibility. Technical difficulties in performing the test, followed by Paigen and co-workers' (1977) report that they could not demonstrate altered arylhydrocarbon hydroxylase inducibility among offspring of lung cancer patients, cast doubt on the usefulness of this test as a risk predictor. However, questions of genetic susceptibility remain since there has been a new report of impaired respiratory function among relatives of lung cancer patients (Cohen, et al., 1977). Impaired forced expiration in first degree relatives of lung cancer patients was emphasized when adjustments were made for smoking, race, sex, and other confounding factors. While this is a new finding which has not yet been corroborated by other studies, it is consistent with an epidemiologic study carried out in the 1960's which showed a familial pattern for lung cancer risk. Estrogen, both exogenous and endogenous, is another cancer risk factor which has been of great interest recently. Weiss (1977) report a two-to five-fold increased risk of endometrial cancer among menopausal women receiving stilbestrol for various medical indications. Endogenous estrogen levels are particularly interesting in relation to breast cancer. It has been postulated that elevated levels of certain estrogen fractions occurring early in life may increase breast cancer risk. Familial patterns of breast cancer risk have been demonstrated, particularly among women who get breast cancer before the menopause. A study of teenage daughters of premenopausal women with unilateral breast cancer has shown elevated levels of estrogens and progesterone during the follicular phase of the menstrual cycle (Henderson, 1977). More than half the daughters of women with breast cancer, compared with about one-sixth of the daughters of normal women showed elevated levels of prolactin and total estrogen on at least one occasion. A follow-up study of daughters of women with bilateral breast cancer has produced preliminary observations consistent with the above findings. This study is expected to show whether the degree of elevation of hormone levels correlates with level of breast cancer risk.

The low rates and excellent survival of Japanese women with breast cancer led some to suspect that women with low initial risk might have some innate resistance to the disease which would give a survival advantage. This was explored among women in Yugoslavia, Wales, the United States, and Japan. Women in Wales and Yugoslavia experienced lower incidence and higher mortality than U.S. women, leading to the conclusion that no correlation between incidence and survival exists (Morrison, 1977).

Environmental carcinogens have also been suspected of a role in breast cancer etiology. This possibility is being investigated through microchemical studies of fluid extracted from normal nonlactating breasts (Petrakis, 1978). Nicotine was demonstrated in breast fluid samples at greater levels than in blood plasma in specimens taken from women 15 minutes after smoking a single cigarette. The level of nicotine in breast fluid increased with cigarette consumption. Cotinone, a metabolite of nicotine, was demonstrated in breast fluid in concentrations equivalent to those in blood plasma. These investigators have found and reported a variety of substances (barbiturates, fatty acids, test compounds) administered orally or parenterally are also rapidly secreted into breast fluid. They believe the secretion of exogenous susbtances into breast fluid may be a general phenomenon.

The debate over mammography as a screening procedure which may carry radiologic risk for breast cancer among women under 50 has led to consideration of using initial mammographic parenchymal patterns to classify women by breast cancer risk categories (Wilkinson, 1977). A study of women in Los Angeles who had mammography prior to breast cancer was instituted to determine the effectiveness of the Wolfe classification in predicting breast cancer risk. It was found that the Wolfe classification when used by individuals accustomed to the radiographic techniques was the single most accurate predictor of risk among premenopausal women. However, the accuracy deteriorated when films were interpreted by readers accustomed to different contrast levels. It was concluded that a national standard for mammographic technique would enhance the utility of the Wolfe classification for assessing the breast cancer risk of women under 50 years of age.

Other environmental agents have been implicated as risk factors for cancer. A New York study of angiosarcoma of the liver suggests that environmental exposures to hazardous chemicals may be important (Brady, 1977). They were able to demonstrate direct exposure to substances known to cause angiosarcomas (arsenic, vinyl chloride, and thorium dioxide) in less than half the cases. However, several cases resided within a mile of plants releasing arsenic or vinyl chloride into the environment. The absence of a sex gradient in New York, and an incidence rate higher than the U.S. rates, also suggest that environmental contamination is more important than may have been recognized.

Few human neoplasia are now thought to be caused by infectious agents. However, hepatoma may be an exception and is an important cause of death in countries where infectious hepatitis is extremely prevalent and both chronic carriers and chronic hepatitis are common. The discovery that the human bedbug is a potential vector for hepatitis B is important in international health and will be a significant factor in the control of hepatitis infection (Wills, 1977). It may be many years before the influence on hepatoma can be directly demonstrated. This is an instance in which cancer research has produced an important side product.

Another neoplasm for which a communicable etiology has been postulated is Hodgkin's disease among the younger age groups. Gutensohn (1977), after a comprehensive review, hypothesized that Hodgkin's disease may be similar to paralytic polio--a rare manifestation of a common disease. If this is true, she postulates increasing incidence in the U.S. over the coming decade, reflecting the improved standard of living and small family size. The potential role of prior infections was also investigated by Paffenbarger, (1978), in a study of male graduates of Harvard and the University of Pennsylvania. He observed that the characteristics in youth which were predictive of Hodgkin's disease and lymphatic leukemia were parallel, but opposite to those observed for non-Hodgkin's lymphoma, myeloid leukemia, and unspecified leukemia. Exposure to common childhood infections was associated with decreased risk for Hodgkin's disease and lymphatic leukemia, while varicella was associated with increased risk of other malignant lymphomas and unspecified leukemia; tonsillectomy was associated with increased risk of unspecified leukemias and obesity with Hodgkin's disease while leanness was associated with increased risk of other lymphomas. High use of coffee and smoking were associated with increased risk of Hodgkin's disease, myeloid leukemia, and lymphatic leukemia. The deaths from malignancies of the skin were also studied. Outdoor exposure was associated with increased risk of malignant melanoma.

Again, the possibilities of genetic and environmental interaction have been of interest. A study of the immune functions in healthy relatives of families with multiple lymphoreticular neoplasms compared with similar functions in families with no known history of cancer was reported (Dworsky, 1978). The lymphoma family group had significantly elevated serum level of IGM and diminished response to the Candida albicans skin test antigen and the T-cell mitogen concanavalin A. Those individuals who had EBV-viral capsid antigen titer levels of 160 or greater had lower responses to mitogens. This is consistent with previously documented risk of certain neoplasia, including lymphomas, among immunodeficient individuals with certain recessive genetic diseases.

Emphases and Projections

As the more common cancers become better characterized for demographic risk factors, two results become apparent: the studies of these common sites become more refined and the more unusual sites such as brain and multiple myeloma are examined. The cancer maps published by NCI stimulated a series of proposals to do geographic comparisons in various areas of the United States, but these have not generally fared well during review. Similarly, technical problems have interferred with occupational and dietary studies. It seems most likely that combined genetic/epidemiologic studies using markers of susceptibility or exposure will emerge as the most productive avenue of investigation. If this is true, improved communication between scientists working on mechanisms of disease and those developing biologic markers and epidemiologists/geneticists will be necessary. Some trend in this direction has recently been sensed, but there has been no major move.

Other Program Activities

Again this year, a major effort has gone into the feasibility study of a cancer patient data system's developing among comprehensive cancer centers. The system has been brought to early operational phase through funding for a Statistical Analysis and Quality Control (SAQC) Center at the Fred Hutchinson Cancer Center in Seattle, complemented by a series of grants to most comprehensive cancer centers. With the organization of working committees, the acceptance of a trial data set, and the development of a quality control framework, this activity seems to have been initiated.

Benefits which are readily apparent include improved patient registration at the centers. With this has come better statistical management of the data and improved surveillance of patients eligible for and entered on various clinical protocols. It has led to improved communication among the personnel of various centers, so that exchange of information about best statistical packages and computer systems could be developed.

It is possible that this system could also result in collaborative epidemiologic studies and standardized questionnaires for eliciting information about known risk factors. However, this and other potential benefits from this system will depend in large measure on the interests and qualifications of those who lead the program in the immediate future.

New activities initiated during the year should result in improved coordination of epidemiologic research within the NCI. These included a series of staff workshops concerned first with data systems (CCPDS, SEER, cancer control, etc.) and later with epidemiologic research and occupational studies. The development of an NIH Epidemiology Committee has also enhanced communication among the Institutes and focused attention on some of the major problems for epidemiologic research. While the primary emphasis is on intramural activities, there are several benefits which are already apparent from discussion of mutual problems.

In the absence of a generally accepted forum for reporting cancer epidemiologic and preventive research, several trends seem to be developing. The Society for Epidemiologic Research (SER) Meetings in June attracted a series of cancer activites (scientific sessions as well as program workshops), and a new organization, the American Society for Preventive Oncology (ASPO), meeting in the early spring also offered an outlet for cancer epidemiology. The more traditional cancer meetings (American Association for Cancer Research, American Society for Clinical Oncology, and American Cancer Society) have not developed an epidemiologic focus.

CANCER EPIDEMIOLOGY PROGRAM

(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
TRADITIONAL	33	$3,747	16	$1,776	49	$5,523
PROGRAM PROJECTS	5	2,912	1	797	6	3,709
CONFERENCES	0	0	3	138	3	138
YOUNG INVESTIGATORS AWARDS	0	0	1	33	1	33
TOTAL	38	$6,659	21	$2,744	59	$9,403

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VIRAL ONCOLOGY PROGRAM

Description

Viral Oncology concerns the role of viruses as a primary or contributory factor in the cause of cancer and the consequences of this for the identification of susceptible individuals, early diagnosis, and developments of new modes of prevention and treatment. Investigations comprise studies at the cellular and molecular levels, as well as the level of the host, in model systems and in man. They include, among others, the nature and mechanism of neoplastic transformation and its expression at all levels of biological organization, the biology and chemistry of the cell-virus and host-virus relationship, the pathogenesis, pathology and immunology of virus-induced neoplastic diseases, and basic research relevant to cancer, such as investigations of gene expression and cell regulatory functions in which viruses are important tools.

Although so far viruses have not been unambiguously identified as a causal element in human malignancies, there is abundant evidence that a wide variety of viruses can transform normal cells to malignant cells *in vitro*, occasionally with great efficiency, can readily induce cancer in various species of animals, and are frequently the cause of their natural malignant diseases. For these reasons, viruses continue to be a powerful stimulus to investigate their role in human cancer.

The key problem which the virus approach to cancer is most likely to solve concerns the mechanism whereby a normal cell is converted to a cancer cell, and the elucidation of the fundamental change(s) in a cell which renders it no longer subject to normal physiological control, in short, a cancer cell. Not only are the viruses powerful transforming agents, but perhaps of equal importance they provide techniques and specific markers which allow investigators to follow the intricacies of the process of neoplastic transformation in the cell with relative ease. In this regard, viruses, particularly tumor viruses, (because they are minimally disruptive and certainly less likely to kill the cells they infect), are almost ideal either as models or as probes for the investigation of various more-or-less normal cellular processes as well, such as the analysis of gene structure and function, the mechanism of flow of genetic information in the cell, and the control and regulation of gene expression. Significant advances in these areas will be discussed as well as others which also have their origin in virological concepts and techniques.

Recent Accomplishments

Transformation Gene Products:

A major advance in elucidating the mechanism of carcinogenesis is the identification of a protein product of the so-called *src* gene of the avian sarcoma virus (an RNA virus), believed to be responsible for transforming normal chicken fibroblasts to sarcoma cells *in vitro*, and for inducing cancer in chickens. This protein is not a constituent of the virus but rather a product coded by it. Defective viruses lacking the *src* gene induce neither the protein nor sarcoma. Thus, the protein, which has a molecular weight of about 60,000, is transformation-specific (Brugge and Erikson, 1977). The same protein was subsequently identified in an in vitro protein-synthesizing system when supplemented with appropriate constituents of the nondefective virus but not when supplemented with constitutents of the defective virus lacking the src gene (Purchio, Erikson, and Erikson, 1977). More recently, the protein was characterized as a kinase, i.e., a phosphorylating enzyme (Collett and Erikson, 1978). Its precise function in the transformation event remains to be determined.

Progress in identifying the transforming proteins coded by DNA viruses is also taking place. In the case of Simian Virus 40 (SV40), a nuclear antigen (T antigen) specified by one of the three SV40 genes (the A gene) is involved in transforming fibroblasts to tumor cells and in the induction of cancer in model animal systems. The T antigen is a protein with a molecular weight of 94,000 daltons. Recently, a complexity has been added to this picture in that an immunologically related protein of 17,000 daltons ("small t") appears also to be involved in transformation, although its exact role and relationship to "big T" is unclear as yet (Prives et al, 1977, Crawford et al 1978, Tegtmeyer and Berg 1978).

The importance of these studies is that they may lead to the formulation of general principles applicable to the biogenesis of neoplasia in general, and the possibility that gene products of this sort may be useful reagents in the prevention or treatment of cancer. In this regard, protective vaccination with a virus-coded product has been successful in the case of cat leukemia, a naturally occurring disease in an outbred species. Thus, vaccination with formaldehyde-treated leukemia cells was effective, whereas vaccination with the virus itself was not. It is believed that a virus-coded protein (FOCMA) on the cell surface is the antigen responsible for conferring protection. Perhaps it is more than coincidental that purified FOCMA has a molecular weight of 65,000, (Stephenson et al, 1977) approximating that of the src gene product of the avian sarcoma virus. This example illustrates the broad concept of investigating transformation gene products for prevention of cancer.

Origin of Avian Sarcoma Viruses:

Genetic recombination between viruses, and between viruses and cellular genes, is known to occur. Only recently, however, has it been surmised that recombination between the genes of a defective nontransforming virus and "normal" cellular genes could be the mechanism whereby transforming viruses are generated. Transformation-defective avian viruses (mutants lacking the src gene in whole or in part) were inoculated into day-old chicks. From every sarcoma that subsequently developed, a fully transforming sarcoma virus was recovered (Hanafusa et al, 1977). The possibility that the recovered sarcoma virus was really present in subliminal amounts in the original defective virus preparation was excluded as an explanation of the results. It was inferred, therefore, that the new virus was generated from the interaction of the genomes of the defective virus and chicken cells. The location and exact nature of the genes of the chicken cell which conferred sarcoma properties to the defective virus have yet to be elucidated.

Viral DNA Nucleotide Sequence

The entire sequence of the DNA of the SV40 virus, consisting of 5,224 pairs of nucleotides, has now been determined by American and Belgian investigators simultaneously and independently (Reddy et al, 1978, Fiers et al, 1978). This tour de force, achieved with the assistance of a remarkable advance in the science of sequencing DNA (Maxam and Gilbert, 1977) will make it possible to relate specific biological functions to particular sequences of the genome, including its transforming function, and will assist in identifying the gene products (proteins) directly responsible for these functions.

Splicing and Gene Expression:

A central problem in the biology of cells and of cancer concerns the mechanism whereby the expression of genes is regulated. All the cells of a given organism, including its cancer cells, presumably contain the same complement of genes, yet the various kinds of cells produce different products and exhibit different properties. Thus, the expression of genes is somehow controlled and regulated in the cell. In cancer, it is believed, there is a disturbance in the normal regulation of gene function. A recent discovery has provided insight into a novel mechanism of gene regulation which has thrown some light as well as additional complexity on this phenomenon. In the flow of information from DNA to RNA (transcription), and RNA to protein (translation), it has been found that contiguous sequences of DNA are not necessarily faithfully transcribed to the homologous RNA (as appears to be the case in bacteria); or, if they are faithfully transcribed, then portions of the RNA are subsequently deleted and the remaining pieces "spliced" together to form the functional messengers (mRNA's), for which there is good evidence. Whatever the details, the net effect is that the resulting messengers consist of sequences transcribed from widely separated sections of the DNA of the cell. Clearly, there is selectivity and choice in this process, thus exercising control over what kinds of DNA sequences are ultimately expressed as proteins, an important aspect of gene regulation. The precise mechanism of this process, which has been observed in a number of viral-cell systems and has also been shown to occur in normal, uninfected cells, is under intensive investigation in many quarters. "Splicing" was discovered independently and essentially simultaneously by a number of investigators (among them, Hsu and Ford, 1977; Aloni et al, 1977; Berget, Moore, and Sharp, 1977; Krzyzek et al, 1978; and Mellon and Duesberg, 1977).

Biochemical Transformation:

Functional viral or proviral DNA--either the intact molecule or a fragment of it--can be transferred from one cell to another by appropriate techniques. If the information so transferred is oncogenic, the cells may be transformed to tumor cells. If, however, the information is nononcogenic, transformation may still occur in the sense that some heritable alteration of the cell takes place. Thus, cells appropriately treated with herpes simplex virus DNA may become transformed oncogenically (rarely), or nononcogenically. Nononcogenic transformation has been detected by the acquisition of some activity; e.g., that of a specific thymidine kinase (tk) that the cell previously lacked. Pellicer, Wigler, and Axel (1977) have determined that the gene responsible for this particular biochemical transformation is stably integrated in the cell's DNA. Further, even though this gene is a vanishingly small part of the DNA of the cell, unfractioned DNA from the transformed cell nevertheless permits transfer of the new tK function. This success suggested the feasibility of transferring indigenous (i.e., normal) genes from one cell to another. This has now been achieved. They have shown (Wigler et al, 1978) that the indigenous tk genes from various species of animals can be transferred to mouse cells that lack the gene. In principle, their procedure can be applied to any gene, either viral or cellular, for which methods for detection of a newly acquired property are available. Such an approach opens the way to determining the function of various DNA sequences of the complex genome of animals, including that of humans, a notable development in the continuing analysis of gene action.

Recombinant DNA:

Recombinant DNA technology has enormous theoretical and practical promise. The stage has now been reached where the entire coding sequence for insulin has been successfully incorporated into a bacterial plasmid (Ullrich et al, 1977), as follows: Insulin RNA (mRNA) was isolated from rat pancreas, complementary DNA (cDNA) prepared with the aid of the RNA tumor virus reverse transcriptase, and cloned in *E. coli* in order to synthesize large quantities for analysis. Whether the cloned insulin gene can be transcribed and translated to make a product from which functional insulin can be prepared, remains to be determined. The structural gene for rat growth hormone (somatotropin) has similarly been prepared from the RNA of rat pituitary cells and amplified in *E. coli* (Seeburg et al 1977). The investigators sequenced the DNA by well established procedures, from which they deduced the complete amino acid sequence of the hormone, hitherto not completely known. Aside from facilitating research on the regulation of the growth hormone gene, the authors believe that their procedure "will prove useful in developing systems for providing somatotropin, a hormone that is currently in short supply." Shine et al (1977), using analogous procedures have also cloned human chorionic somatomamotropin ("placental lactogen"), and, as before, the primary structure of the hormone was deduced from an analysis of its nucleotide sequence. The development of recombinant DNA science was and will continue to be heavily dependent on virological and microbiological techniques.

Growth Control:

Last year's report discussed a cell surface glycoprotein termed LETS (Large External Transformation Sensitive), whose loss from virus-transformed cells correlated with their tumorigenicity. A further development (Ali, et al 1977) is that addition of this protein to transformed cells restored a number of properties characteristic of normal cells, such as increased adhesion to substrate, normalized cytoskeleton, and cell shape. In a related but independent investigation, Lipkin, Knecht, and Rosenberg, (1977), have also found that a glycoprotein, MCIF (Melanocyte Contact Inhibitory Factor) isolated from the media in which normal cells had been cultured, but absent from media of malignant cells, restored contact inhibition of growth and is, in fact, a selective and potent inhibitor of tumor cells. An understanding of these phenomena could, as emphasized by these investigators and brought out in a recent conference (Stansly 1975), provide the basis for another approach to cancer therapy, i.e., the possibility of modifying the behavior of cancer cells, as opposed to their destruction, as a possible avenue to treatment.

Emphases and Projections:

The main goals of the virological approach to the Cancer Program continue to be the elucidation of the mechanism of oncogenic transformation, particularly at the cellular and molecular levels, and the analysis of the cascade of events that result in and characterize the cancer cell.

The value of viruses, especially tumor viruses, in unravelling the mechanism of gene control and regulation, as probes of cell structure and function, and as models of replicating genetic entities has been amply demonstrated and documented (Kolata, 1977). These approaches to cell biology will surely continue to be productive for years to come.

The fact that certain viruses are causal agents in naturally occurring malignant diseases of animals will continue to be a powerful stimulus to determine their role in human cancer, abetted also by provocative findings of endogenous information in the tissues of man related to known tumor viruses (Keydrer et al, 1978). The practical success of viruses or their products in preventing naturally occurring malignant diseases (Marek's Disease of chickens, cat leukemia), is another stimulus to continued efforts to determine the role of viruses in analogous human diseases.

Recombinant DNA technology largely resulted from virological concepts and techniques. It is expected that investigators in the Viral Oncology Program will continue to develop the field both for their application to fundamental problems in oncology, and for possible practical procedures for the synthesis of valuable substances for research and treatment presently in short supply, such as hormones.

Other Program Activities:

The Viral Oncology Program supports workshops and conferences by means of grants and contracts; these included, during fiscal year 1978: (1)"Seminars and Workshops in Techniques in Cancer Research" at Aspen, Colorado, covering various aspects of cell control mechanisms, RNA tumor viruses, herpes viruses, and other etiological factors in carcinogenesis; laboratory workshops included cell fusion, liposome incorporation, immunofluorescence and immunoperoxidase assay, chromosome banding, mutagenesis, and nucleic acid hybridization; (2) four workshops at Cold Spring Harbor covering the transformed cell, molecular cytogenetics, oncogenic viruses, and yeast genetics; (3) a Gordon Research Conference on Cancer at Colby College, New Hampshire; (4) a Cold Spring Harbor symposium on Chromatin, and (5) a conference on persistent viruses at Keystone, Colorado.

Other activities included (1) participation in the deliberations of the Virus Cancer Program Coordinating Committee; and (2) coordination and organization of conferences and workshops on metastasis and exchange of scientists in connection with the U.S.-Japan Cooperative Cancer Research Program. The latter resulted in two books.*

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* _Progress in Cancer Research and Therapy, Vol.5_: _Cancer Invasion and Metastasis_: _Biologic Mechanisms and Therapy_. Edited by Day, S.B., Laird, W.P., Stansly, P.G., Garrattini, S., and Lewis, M.G. Raven Press, New York, 1977.

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VIRAL ONCOLOGY PROGRAM

SUMMARY BY SUB-CATEGORY
(Dollars in Thousands)

	NONCOMPETING NO.	NONCOMPETING AMOUNT	COMPETING NO.	COMPETING AMOUNT	TOTAL NO.	TOTAL AMOUNT
RNA TUMOR VIRUSES						
AVIAN	37	$3,557	16	$1,077	53	$4,634
MURINE	22	1,721	14	994	36	2,715
MAMMARY CANCER	6	622	2	201	8	823
OTHER	7	576	2	197	9	773
TOTAL	72	$6,476	34	$2,469	106	$8,945
DNA TUMOR VIRUSES						
POLYOMA	8	$ 817	3	$ 240	11	$1,057
SV40 AND RELATED VIRUSES	38	2,689	17	1,548	55	4,237
HERPES	21	1,885	6	410	27	2,295
ADENO	12	926	6	487	18	1,413
OTHER	8	614	3	204	11	818
TOTAL	87	$6,931	35	$2,889	122	$9,820
RELATED AND SPECIAL PROGRAMS	15	$1,742	10	$ 854	25	$2,596
PROGRAM PROJECTS AND CENTERS	14	9,308	4	1,773	18	11,081
CONFERENCES	2	110	0	0	2	110
YOUNG INVESTIGATORS AWARDS	0	0	1	33	1	33
TOTAL	190	$24,567	84	$8,018	274	$32,585

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NATIONAL ORGAN SITE PROGRAMS BRANCH

The National Organ Site Programs consist of grant-supported National Projects of targeted cancer research. Each Project is a planned research effort oriented toward cancer at a specific organ site. Currently there are National Organ Site Projects concerned with cancers of the urinary bladder, large bowel, pancreas, and prostate. The planning, direction, and coordination of each Project are provided at a Headquarters institution other than the NCI. A National Project Director, who is not an employee of NCI, is assisted in planning and administration by a Headquarters staff and by a Working Cadre of active research scientists recruited from institutions throughout the Nation. Grant applications are received by the Headquarters and are reviewed by the Working Cadre and by the National Cancer Advisory Board. Applications which are judged scientifically meritorious and relevant to the aims of the Project are recommended to the NCI for funding.

Each National Project Director is a recognized clinical or laboratory scientist with a strong interest in, and professional identification with, a specific organ site cancer. The National Bladder Cancer Project is under the direction of Dr. Gilbert H. Friedell, St. Vincent Hospital, Worcester, Massachusetts; the National Large Bowel Cancer Project, Dr. Murray M. Copeland, M. D. Anderson Hospital and Tumor Institute, Houston, Texas; the National Pancreatic Cancer Project, Dr. Isidore Cohn, Jr., Louisiana State University School of Medicine, New Orleans, Louisiana; and the National Prostatic Cancer Project, Dr. Gerald P. Murphy, Roswell Park Memorial Institute, Buffalo, New York.

NATIONAL BLADDER CANCER PROJECT

Description

The National Bladder Cancer Project is a coordinated research effort which sponsors and encourages basic and clinical research directed towards improving techniques for detecting bladder cancer, finding better methods of treating the disease, identifying carcinogenic factors and developing means of minimizing their effect, and finding means of protecting high-risk populations.

With the control of bladder cancer as the ultimate goal, a multidisciplinary program has been developed to stimulate new research areas. Knowledge of the demographic, biological, and environmental factors associated with the disease will permit identification of groups at high risk. The natural history of the disease is being investigated through studies on carcinogenic mechanisms, host response and resistance, and markers of preneoplastic epithelial cell changes. Developing methods to detect and diagnose the disease at an early stage is an important aspect of the research effort. This emphasis assumes that the earlier the diagnosis, the more favorable the prognosis and the more effective the treatment. Bladder carcinoma includes a heterogeneous group of tumors with varying degrees of malignancy. Various methods of classifying and staging the disease are being evaluated to enable utilization of the most appropriate therapy. To improve results of treatment, several avenues of clinical research are being pursued, including adjuvant therapy, radiation therapy, chemotherapy, and immunotherapy.

Two collaborative efforts are being supported by the NBCP for prospective studies of patients with bladder carcinoma--the National Bladder Cancer Collaborative Group A and the National Bladder Cancer Project Confederation. Collaborative Group A consists of ten institutions: Massachusetts General Hospital, University of Tennessee, Virginia Mason Research Center, Rush Presbyterian-St. Luke's Medical Center, St. Vincent Hospital, University of Oregon, Medical College of Virginia, Roswell Park Memorial Institute, University of Iowa, and Georgetown University. The Confederation consists of four institutions: Mayo Clinic, Memorial Sloan-Kettering Cancer Center, M.D. Anderson Hospital, and UCLA School of Medicine. Collaborative Group A is continuing follow-up studies of patients which were entered into one or more of four protocols--a surveillance of all patients admitted to the participating institutions with bladder carcinoma; a study of multiple mucosal biopsies from patients with frank tumor or positive cytology; an evaluation of intravesical therapy with thio-TEPA; and a study comparing radiation therapy alone to radiation therapy plus cystectomy for invasive carcinoma. The group is in the process of initiating three new protocols--a Phase III study of systemic chemotherapy in patients with metastatic bladder carcinoma; a study of systemic chemotherapy as adjuvant to definitive radiation and surgical therapy of invasive bladder carcinoma; and a study of chemoprevention of recurrence in patients with completely resected low-stage lesions. The Confederation is initiating Phase II studies of four different drugs or combinations of drugs along with a common protocol study of cis-platinum in advanced metastatic carcinoma patients.

Accomplishments

The proceedings of the August 1977 National Bladder Cancer Conference sponsored by the National Bladder Cancer Project were published in Cancer Research, Volume 37, Number 8, Part 2, Pages 2743-2973. Five sessions explored the current state of knowledge concerning (1) the assessment and management of deeply invasive and metastatic lesions, (2) recognition of early bladder cancer and premalignant epithelial changes, (3) classification of tumor and host, (4) management of early bladder lesions, and (5) cause and prevention of bladder cancer. Many of the contributions have been selected from research performed under the auspices of the NBCP including Bean 1977; Farrow *et al*, 1977; Friedell 1977; Irving 1977; Jacobs *et al*, 1977; Kahan *et al*, 1977; Leighton *et al*, 1977; Melamed *et al*, 1977; Merk *et al*, 1977; and Paulson *et al*, 1977.

Prognostic indicators of tumor aggressiveness and host responsiveness were reported. The presence of marker chromosomes in papillary cancers indicates the likelihood of recurrence and progression (Sandberg, 1977). Skin tests with dinitrochlorobenzene, which become negative as the amount of tumor increases but return to normal upon removal of tumor, assess the overall competence of the host immune defense (Fahey, Brosman, and Dorey, 1977).

The murine model has been used to evaluate intravesical and systemic chemotherapy of bladder cancer (Soloway, 1977). Implantation of suspended tumor cells upon the denuded urothelial surface was significantly reduced in mice by intravesical epodyl and epipodophyllotoxin, and less so by thio-TEPA. Several drugs were effective against primary and transplanted FANFT-induced bladder tumors, including cyclophosphamide and cis-platinum; combinations were more effective than the single agents. A cautionary note was the finding that systemic BCG immunotherapy often produced tumor enhancement.

The role of suppressor T-cells in causing a poor immune response, which has been well-documented in murine models, has now been demonstrated in a patient with multiple recurrent bladder cancer (Bean *et al*, 1977). Cell-mediated immunity can be demonstrated briefly during the progression of a tumor by rejection of a second inoculum *in vivo* or by a cytotoxic response against tumor cells *in vitro*; it is the responsibility of thymus-derived lymphocytes termed effector T-cells. These cells are under the immunoregulatory influence of amplifier (helper) T-cells and suppressor T-cells. Just as in murine models, the newly discovered human suppressor T-cells are genetically restricted; this means that they can only suppress other T-cells which share a gene region of the major histocompatibility complex. It is proposed that with prolonged exposure to tumor antigen, the balance between helper and suppressor cells tips some patients toward excess proliferation of suppressor T-cells. This leads to immunodepression and loss of cell-mediated tumor immunity. Understanding these mechanisms will be a prerequisite for developing rational approaches to immunotherapy.

Entry of new patients into some of the first protocols of National Bladder Cancer Collaborative Group A--surveillance, multiple biopsies, intravesical therapy, and definitive therapy for invasive carcinoma--has been terminated. However, follow-up continues until adequate data are accumulated to permit conclusions to be drawn. The strategy which was developed for defining prospective longitudinal studies along with intermediate progress reports has been published (National Bladder Cancer Project Collaborative Group A, 1977, a,b,c). Although further data must be collected before final analyses can be made, there is evidence that superficial transitional cell carcinoma has a recurrence rate of more than 30 percent within the first year after complete removal of the lesion by transurethral resection; there is evidence that transitional cell carcinomas are more consistently detected by cytologic evaluations of bladder-washing specimens than by evaluations of voided specimens; and evidence showed thio-TEPA to produce responses of about 33 percent in this collaborative effort, confirming the experiences of others.

Emphases and Projections

A major effort will be made in the coming year by the National Bladder Cancer Collaborative Group A to assess the results of the first four protocols--surveillance, multiple biopsies, intravesical therapy, and definitive therapy for invasive carcinoma--both for information which can be interpreted from the analyses and for generating new hypotheses about the course of the disease(s) which can be translated into new and better intervention strategies. The specific clinical efforts will be directed at three protocols. Cis-platinum will be compared to cis-platinum plus cytoxan for definitive chemotherapy in metastatic disease. Cis-platinum will also be tested as an adjuvant to definitive radiation plus surgical therapy. Finally it will be seen if 13-cis-retinoic acid can prevent the recurrence of superficial disease. The National Bladder Cancer Project Confederation will concentrate on conducting Phase II studies with drug combinations in metastatic disease and planning an adjuvant chemotherapy study in invasive disease patients definitively treated with radiation and surgical therapy.

Diammine dichloroplatinum (cis-platinum) is one of the most effective chemotherapeutic agents yet developed against bladder cancer. In tests on the FANFT mouse model, a striking additive effect has been found between radiation therapy and cis-platinum therapy. Because of the major side effects of nausea and severe vomiting which accompany intravenous cis-platinum administration, intravesical cis-platinum instillation has been studied. No absorption was found in extensive studies on dogs. Subsequent Phase I pharmacological studies in humans have shown no local or systemic toxicity. These preliminary findings indicating effectiveness against carcinoma *in situ* are being explored further.

Evidence has been produced in experimental animals that carcinogenesis of bladder tumors is a two-stage process with initiation followed by promotion. In theory, initiators would induce irreversible changes in target cells, while promoters would cause proliferation of the altered cells to produce tumors. In practice, potent carcinogens may act as both initiator and promoter, so it is necessary to utilize low enough doses to elicit only the initiating action in order to test other compounds for their promoting action. When young rats were fed the carcinogen FANFT for 30 weeks, all developed bladder cancer. If FANFT feeding was stopped after six weeks, there was a mild transient hyperplasia and only a few animals developed tumors after two years. If saccharin, a nonnutritive sweetening agent, or DL-tryptophan, an essential amino acid whose metabolites have been implicated in human bladder cancer, were fed following six weeks of FANFT, a high incidence of bladder cancer resulted. At the doses used, saccharin produced more tumors in a shorter time than tryptophan. Neither saccharin nor tryptophan without prior FANFT feeding produced bladder tumors. It appears that both saccharin and tryptophan have significant tumor-promoting effects after subtumorigenic doses of a potent carcinogen. This points the way for future testing of other possible promoters in bladder carcinogenesis.

Although large quantities of tumor can be obtained from patients with advanced invasive disease, it has been difficult hitherto to obtain adequate quantities of low-grade, low-stage tumor to study. This is important because early tumors may possess different antigenic makeups and respond differently to chemotherapeutic agents than advanced tumors. A unique tool for the propagation and study of tiny early tumors is the athymic nude mouse, whose defective immune system allows the growth of human cancer cells to 30-fold mass increase, equivalent to the yield of 7,500 tissue-culture dishes. Retention of human identity is proved by karyotypic analysis, production of human isoenzymes, and susceptibility to diptheria toxin. This relatively abundant material can be employed in the attempted isolation and identification of unique tumor antigens. Once obtained, these antigens could be used to develop immune diagnostic procedures and to explore the possibility of specific immunotherapy. The athymic nude mouse also offers a promising model for testing chemotherapeutic agents against the cancer cells of individual bladder cancer patients.

One difficult challenge for diagnostic cytology is the detection of small papillary bladder tumors. According to current estimates, 84 percent of carcinoma _in situ_ can be diagnosed by cytological screening, whereas only 22 percent of papillary Grade I carcinomas can be detected in this way. Cystoscopy can complement cytology, but there are still cases where both methods give false negatives. As it stands, one could infer that _more_ than 30 percent of all people now have bladder cancer and all but 30 percent are missed by cytology. For this reason attention is being focused on the development of additional diagnostic modalities such as scanning electron microscopy and automated cytology methodologies.

Other Program Activities

An Investigators' Workshop was held in Sarasota, Florida, from January 29 to February 1, 1978. Its purpose was to promote communication among investigators, to acquaint preclinical scientists and clinicians with each others' research problems and opportunities, to stimulate new ideas, and to encourage collaborative efforts. Poster sessions followed by discussions were held in immunology, pathology, and carcinogenesis. There were miniseminars in pathology, epidemiology, and statistics. Speakers explored tumor immunology including immunosuppression and immunodiagnosis, urinary cytology, chemotherapy, and carcinogenesis.

In collaboration with the International Cancer Research Data Bank Program of the National Cancer Institute, 202 abstracts on bladder cancer published in 1977 through November 1 were organized and printed in a pamphlet entitled "Selected Abstracts on Bladder Cancer," which is available upon request.

A state-of-the-art workshop conference on screening of bladder cancer, sponsored by the Division of Cancer Control and Rehabilitation of the National Cancer Institute, was held on December 5-6, 1977, at Dulles International Airport, Virginia. Dr. Gilbert H. Friedell, National Bladder Cancer Project Director, chaired the conference. Many of the participants and screening committee members have been, or are currently, associated with the National Bladder Cancer Project.

NATIONAL BLADDER CANCER PROJECT

(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
22	$2,588	22	$1,782	44	$4,370

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NATIONAL LARGE BOWEL CANCER PROJECT

Description

The National Large Bowel Cancer Project, with headquarters at the University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, sponsors multidisciplinary basic and clinical programs of research designed to examine the biology and promote the control of colon and rectal cancer. These objectives are pursued by encouraging research grants in a spectrum of programs designed to: (1) identify the causes of large bowel cancer and their inhibitors, (2) identify and clarify biochemical and molecular controls, (3) identify individuals at high risk, (4) promote early diagnosis and prevention of large bowel cancer, (5) apply modern pharmacologic methods in development of new chemotherapeutic treatments, (6) apply modern tumor immunobiology in development of diagnostic markers, methods of treatment, and prevention of large bowel cancer, and (7) examine clinical research treatment programs.

Knowledge derived from these areas of investigation will have applicability in design of sound research programs to improve management and treatment, and thereby provide the basis for control of this disease.

Accomplishments

Identification of Large Bowel Cancer Causes and Their Inhibitors

Two grantees have made the significant observation that colon carcinogenicity of 1,2-dimethylhydrazine in mice can be completely abolished by concomitant administration of disulfiram and related compounds in the diet (Fiala _et al_, 1977a; Wattenberg and Fiala, 1977; Wattenberg _et al_, 1977a; 1977b). The mechanism for this inhibition has been investigated by metabolic studies (Fiala _et al_, 1977b). These compounds inhibit the N-oxidation of azomethane to azoxymethane and, thereby, prevent the formation of the proximate carcinogen methylazoxymethanol and the postulated ultimate carcinogen, methyldiazonium ion (Fiala _et al_, 1977c). Thus, these results provide a biochemical explanation of Wattenberg's observations on the inhibition of the carcinogenicity of 1,2-dimethylhydrazine (Fiala, 1977; Grab and Zedeck, 1977). An additional conclusion, although still tentative, is that compounds capable of being efficiently metabolized to carbon disulfide would produce similar effects.

The use of germ-free rats as a model for 1,2-dimethylhydrazine (DMH) carcinogenesis has been developed. The observations to date indicate that the male S-D rats are more susceptible to DMH carcinogenesis than female S-D rats. Treatment with Na phenobarbital induces a higher incidence of colon cancer in both male and female S-D rats. In addition, strain differences in susceptibility to DMH-induced colon cancer have been reported (Asano and Pollard, 1977).

Early Diagnosis and Prevention of Large Bowel Cancer

Polyamines in serum have been studied for their potential role as a systemic biological marker of colon and rectal cancer (Nishioka and Romsdahl, 1977), and compared with CEA determination (Nishioka et al, 1977; 1978). While 52 percent of patients with colon and rectal cancer showed elevated CEA values, 60 percent of patients showed elevation of one or more polyamines. However, the two measurements combined yielded a 72 percent positive incidence, indicating that the combined use of these two methods is beneficial.

Application of Modern Pharmacologic Methods in the Development of New Chemotherapeutic Treatments for Large Bowel Cancer

Pyrimidine analogs (FU, FUdR), nitrosoureas (MeCCNU), and anguidin have been tested in transplantable murine colon tumors for potential chemotherapeutic activity. It was observed that 5-fluoropyrimidines were effective inhibitors of DNA synthesis in the mouse model system, although not to the same extent in different tumors (Brockman et al, 1977). Pyrimidine phosphoribosyltransferase activity was markedly increased in colon tumors compared to colon tissue. Further selective enhancement of this enzyme reaction is a potential method for increasing toxicity of FU for colon tumor cells. C^{14}-labeled 5-FU incorporation into RNA of mouse colon tumor and normal tissues has been examined, with the finding that incorporation is low in both types of tissue. Pyrazofurin, which inhibits pyrimidine biosynthesis by blocking the conversion of OMP to UMP, is being examined for its effects on the utilization of other nucleosides (Rose et al, 1977). An examination of the use of pyrazofurin in scheduled combination with pyrimidine analogs may merit future attention in chemotherapy experiments.

Because MeCCNU has proven to be a useful clinical agent for colon cancer, its biochemical effects on these colon tumors and normal tissues were studied. In most instances, DNA synthesis was inhibited more than the synthesis of protein and RNA, inhibition being greater for tumor No. 26 than others; however, this was not due to more extensive alkylation of its DNA. Results suggest that there may be differences in the rate and extent of repair of the DNA and recovery of the tissues (Schabel et al, 1977; Corbett et al, 1977).

PALA and anguidin were studied for their effects on macromolecular synthesis by murine colon tumors as well as normal control tissues (Brockman et al, 1978). Recovery of inhibition following drug administration was variable among these tissues, as well as among the different tumors studied. While the reasons for these variable recovery rates are not now known, such information is being sought to provide a biochemical basis for experimental chemotherapy of mouse colon carcinomas and better treatment regimens for potential application in humans.

Clinical Research Treatment of Large Bowel Cancer

Patients with Dukes' C classification undergoing adjuvant therapy following definitive surgery include 52 individuals receiving BCG alone

(Mavligit et al, 1977c). Additionally, 69 patients received BCG plus 5-FU. The disease-free interval reported for both groups is significantly prolonged as compared to historical controls (P=0.004, P=0.015) (Mavligit et al, 1977a; 1977b). No statistically significant difference was observed between the two treatment arms, although the BCG arm appeared to be slightly better. Overall survival of patients recieving BCG alone exceeded the survival of historical controls.

Application of Modern Tumor Immunobiology in Developing Diagnostic Markers, Methods of Treatment, and Preventing Large Bowel Cancer

Immunological analyses of patients with cancer of the colon and rectum indicate that such individuals exhibit a low response to PPD, Varidase, Monilia, and the mitogens, PHA, PWM, and CCA, in the lymphoblastogenesis assay. The results of these tests, in correlation with age, were investigated in patients with tumors as well as matched individuals without colon and rectal carcinoma (Evans et al, 1977). Except for PPD, a falloff in recall antigen and mitogen sensitivity occurred in individuals above 70 years of age. Mitogens in particular, but also recall antigens, showed an even greater falloff in the presence of tumor. The extent of disease influenced this finding, the influence being most marked in patients with metastatic disease. It has been concluded that this test is probably not sensitive enough in younger patients for responses to be altered noticeably even in the presence of solid tumor.

Studies in 70 patients followed for longer than 200 days after surgery indicate that either Dukes' Classification or CEA greater than 2.5 ng/ml are predictive of future recurrence or re-recurrence. In this series, the reliability of Dukes' Classification and of CEA is additive and the use of both together improves prediction (Evans et al, 1977).

Methodology has been established to adapt cells to serial subcultivation in serum-free medium. This is necessary to avoid the risk of erroneously identifying contaminating serum components which may become incorporated into cultured colonic cells. This will afford a better source of material for the extraction of colonic tumor antigens. Additionally, a hollow fiber culture system has been developed to achieve a histiotypic organoid, glandular, social organization of colon tumor cells *in vitro* (Tom et al, 1977). This more closely approximates the *in vivo* situation and may permit detection of hitherto unrecognized distinctive antigenic factors not demonstrable by cells cultured in monolayer systems.

Evidence has been obtained in a rat colon cancer model that tissue-type specific embryonic antigens associated with these neoplasms are capable of provoking tumor rejection reactions (Nelson and Sjogren, 1977). It has been demonstrated that primary DMH-induced tumorigenesis may be prevented by immunization of the rats to colon carcinoma cells before initiation of carcinogen exposure. The mechanisms related to this observation are being explored as well as potential new approaches for immunoprevention of colon and rectal cancer (Sjogren, 1977).

Identification and Clarification of Biochemical and Molecular Controls of Large Bowel Cancer

In studies to elucidate the alteration in glycoproteins and glycolipids of colon tumor cells, enzymes involved in the biosynthesis and catabolism of these glycoconjugates are being examined. As compared with virally transformed cells, the glycolipid pattern in colonic adenocarcinoma shows more complex and varied alterations (Kim et al, 1977). Six normal glycosphingolipids have been observed in normal colonic mucosa and cancer tissues. Their structures were established by permethylation, glycosidase, and immunological methods. Certain of these are increased, others are decreased, and yet others are unchanged in cancer tissue as compared to normal mucosa. The role of these cell surface alterations in malignant transformation, cell-cell interaction, expression of immunological properties, and other cell surface phenomena represents an important aspect of colon cancer research.

The response of intestinal epithelium to the carcinogen DMH, as measured by thymidine kinase (TK) activity, phosphorylase activity, and adenosine deaminase (ADase) indicates that these enzyme functions are significantly altered in thermolability, aggregation, K_m values, relative substrate specificity, and sensitivity to heat inactivation (Trotta and Balis, 1977a; Trotta et al, 1978). Additionally, colonic polyamines are dramatically changed during DMH administration.

Functions of enzymes were studied in animals receiving antimetabolites. There was a general decrease in activities of all the enzymes examined (Trotta et al, 1978). The effects of drugs differed at different locations of the intestinal tract. There were differences between crypts and villus tips as well. Enzyme activity changes were also observed in the bowel of rats bearing tumor implants (Trotta and Balis, 1978). These studies indicate the remarkable metabolic changes associated with the differentiation of normal rat colonic epithelium (Trotta and Balis, 1977b) and the transition of normal epithelium to adenocarcinoma, and the complexity of the metabolic changes associated with these events.

Studies have been done in vitro to determine what conditions restricting growth affect normal and transformed colon cells (Schiaffonati and Baserga, 1977). It has been observed that normal cells remain viable and attached to the surface while transformed cells die. This information has implications in cancer chemotherapy, since if extrapolated to man, it would indicate that tumor cells would selectively die under conditions that are restrictive for growth. These studies support other observations that decreased caloric intake has little effect on the health of the host and, yet, considerably decreases the incidence and the growth of spontaneous tumors as well as the growth of transplantable tumors.

Studies to elucidate and understand molecular mechanisms which lead to malignant transformation of colonic epithelial cells have been approached by examining alterations in composition, metabolism, and function of nuclear proteins involved in the control of RNA and DNA metabolism (Boffa and Allfrey, 1977; Allfrey, 1977; Karn et al, 1977). In order to carry this out, separation of nuclei and specific nuclear types from intestinal epithelium, from DMH-induced tumors of the rat colon, and from human adenocarcinoma was accomplished (Vidali et al, 1977; Allfrey and Inoue, 1977). Subsequently nuclear protein changes were identified which correspond to successive stages of colon cancer induction by 1,2-dimethylhydrazine. Similar proteins are detected in human colonic adenocarcinomas, but not in normal colonic epithelial nuclei nor in intestinal polyps (Allfrey, 1977). DNA-binding properties of the nuclear proteins represent a potential mechanism for transcriptional control (Boffa and Allfrey, 1977). In this regard, one of the major tumor-associated protein classes has a very high DNA-affinity, a property which will permit additional probes on RNA synthesis and DNA replication.

Administration of 1,2-dimethylhydrazine or MAM acetate has been shown to affect the structure of chromosomal proteins. Radioactive methyl groups from tagged carcinogen were detected in DNA, histones, and non-histone nuclear protein (Boffa et al, 1977; Zedeck and Brown, 1977). It has been established that metabolites of DMH modify the structure of DNA and its associated protein in colonic epithelial cells. This, with other experimental evidence, supports the premise that malignant transformation is basically a chromosomal event which may reflect aberrant interactions between gene-regulatory proteins and DNA. Additional studies indicate that the alkylating carcinogen, DMH, may affect nuclear function by modifying RNA-binding proteins essential for normal transfer of messages from the nucleus to the cytoplasm. In further studies, protein synthesis of colon cancer cells has been shown to be selectively inhibited by sodium cyanate (Allfrey et al, 1977). At similar concentrations of cyanate, there was no appreciable effect on protein synthesis in the livers of tumor-bearing rats, and only a slight suppression of proteins of colonic epithelial cells adjacent to the tumor. The mechanism for this effect is not now known, although approaches to further examine this potentially important aspect are now being formulated. Further analysis of events occurring during malignant transformation has been augmented by development of techniques for microinjection of macromolecules into single cells, particularly messenger RNA, and observations of its subsequent effect on cellular functions (Stacey et al, 1977; Stacey and Allfrey, 1977). Collectively, these studies provide information concerning nuclear protein composition and metabolism associated with the transformation of normal epithelial cells to the malignant state and suggest the direct involvement of gene-regulatory proteins in the aberrant programming of transcription in cancer cells.

Emphases and Projections

The National Large Bowel Cancer Project encourages research in areas which emphasize causation, identification of high-risk individuals, diagnosis, pharmacological control, prevention, and treatment.

During the past several years, animal models have been developed in mice, rats, and hamsters by several different techniques and carcinogenic agents. These models are now being used to: (1) identify and test new chemotherapeutic agents, (2) identify potential inhibitors of carcinogenic substances, (3) examine novel methods of immunoprevention, (4) elucidate events associated with transformation of colon epithelium to precancerous lesions and ultimately overt carcinoma of the large bowel, and (5) examine the effect of dietary factors and influence of microflora in development of large bowel cancer. The use of these animal model systems is expected to expand our concepts and knowledge concerning large bowel cancer in humans and thereby identify means to improve management of patients with this disease.

Animal models for transplantable large bowel cancer and xenografts, as well as development of permanent *in vitro* cell culture lines, have become available for routine use by investigators in this field. The use of different systems and approaches provides the means for examining a variety of biological problems relative to this disease.

It is a goal of the National Large Bowel Cancer Project to emphasize programs directed at prevention of large bowel cancer. These programs will include assessment of: (1) "high risk" populations, (2) dietary factors felt to exert an influence on carcinogenesis of large bowel cancer, (3) development of immunological approaches to prevent large bowel cancer, and (4) prevention by use of currently identified as well as new drugs aimed at interfering with the carcinogenic process.

The National Large Bowel Cancer Project will promote the development of new chemotherapeutic drugs to combat large bowel cancer. Additionally, research will be pursued to identify new targets dealing with metabolic pathways involved in nucleic acid as well as protein synthesis. Cell surface glycoproteins and fundamental aspects of membrane structure will be investigated for potential leads in uncovering abnormal cellular function and augmenting attack by anticancer drugs and immune mechanisms.

While distinct therapeutic projects for human disease will not be specifically emphasized, research proposals with novel and/or innovative approaches will be encouraged and supported in this organ site program.

Other Program Activities

In February 1978, the National Large Bowel Cancer Project sponsored its fourth workshop on large bowel cancer. The subject of this workshop was "Biochemical and Pharmacological Targets of Chemotherapy." This workshop included addresses dealing with the major areas of investigations concerning this topic. The workshop was attended by laboratory and clinical scientists interested in the goals and objectives of the National Large Bowel Cancer Project. An attempt was made to promote a multidisciplinary program, encouraging the participation and cooperation of basic scientists, clinical investigators, and physicians dealing with the management of patients with colon and rectal cancer. It is the purpose of the National Large Bowel Cancer Project Headquarters to utilize information derived from this and subsequent workshops in determining goals and direction of new research applicable to the biology/control of large bowel cancer.

NATIONAL LARGE BOWEL CANCER PROJECT

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
32	$3,242	25	$2,230	57	$5,472

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NATIONAL PANCREATIC CANCER PROJECT

Description

The National Pancreatic Cancer Project currently is in its fourth year of operation. To date, 126 grant applications have been reviewed in the areas of diagnosis, epidemiology, experimental biology, immunology, pathology, and treatment of pancreatic cancer. Twenty-nine projects are in progress. Among these are studies of pancreatic metabolism of carcinogens; a case-control study of pancreatic cancer patients in a large metropolitan area; examination of various diagnostic techniques, including laparoscopy, scanning, and ultrasonography; immunobiologic and immunodiagnostic studies; and pathologic studies.

Accomplishments

Twelve articles have been accepted for publication in major national journals. Five have appeared in print and the remaining seven are accepted for publication (see References).

Reber et al (1977) studied pancreatic secretion in hamsters in which pancreatic cancer had been induced by a carcinogen. Changes in secretion in response to various stimuli antedated the appearance of either the neoplasm or obstruction of the duct, and it was postulated that some of the secretory changes were due to effects of the carcinogen directly on the ductal cells. If study of pancreatic secretion in cancer patients leads to similar results, diagnostic tests detecting early pancreatic malignancy might be based on this information.

Immunologic studies have been used to identify specific tissues as a means of locating abnormalities earlier than by other techniques. Mihas and Spenney (1977) produced an antihuman liver serum and showed this was specific for human liver, as contrasted with liver from other species, and also that it was different from extracts of pancreas.

Wu, Arimura, and Yunis (1977) purified a plasminogen activator secreted by cultured human pancreatic carcinoma cells and identified a number of its characteristics.

Varricchio et al (1977) studied regeneration of rat pancreas after partial pancreatectomy and after chemically induced necrosis of acinar cells. Biochemical evaluation of the factors influencing DNA synthesis were investigated. Rat pancreas tumors induced by carcinogen and human pancreas tumors were grown in nude mice. The specific activity of Histone H1 increases two-to-three fold in regenerating and developing tissues in the rat and two-to-three fold in rat pancreas tumors grown in nude mice.

Bockman et al (1978) studied the proliferation of tubular complexes in rats subjected to chemical induction of pancreatic cancer. Reconstruction of the tubules in three-dimensional models provided insight into the mechanism of tumor development.

Emphases and Projections

Research areas assigned high priority by the National Pancreatic Cancer Project are:

1. Early Treatment
2. Etiology
    A. Epidemiology
    B. Carcinogenesis
    C. Cell Biology
3. Early Diagnosis
    A. Immunology
    B. Tumor Markers
    C. Scanning Techniques
    D. Uptake Studies
4. Clinical Pathology

The Project has identified research in therapy as the area of top priority, and therefore prepared a notice being distributed within the scientific community detailing various protocols believed to be most important in fulfilling the Project's goals in this area. These include phase I and II studies of single chemotherapeutic agents, combinations of chemotherapeutic agents, fast neutron radiation therapy combined with chemotherapy, and combined modality therapy.

Little epidemiologic information on pancreatic cancer is available, but several case-control studies examining socioeconomic, environmental, and dietary factors are in progress with the aim of identifying groups at high risk for the disease.

Early diagnosis continues to be an important research area, with an emphasis on tumor markers, scanning techniques, uptake studies, and immunological studies. The need for reliable animal models is an important goal to fulfill. Several projects working toward refinement of such models will continue, and it is anticipated that several will become available.

Other Program Activities

The National Pancreatic Cancer Project sponsored its second annual joint meeting with the American Pancreatic Association in Chicago on November 3 and 4, 1977. The open two-day meeting, attended by over 200 scientists and clinicians, included two invited talks and 47 presentations by investigators conducting research on the pancreas. A third joint meeting with the American Pancreatic Association is in the planning stage for November 2 and 3, 1978.

The Project has expanded its "Newsletter," which contains information for prospective applicants, reports on progress by grantees of the Project, and an extensive bibliography of articles related to pancreatic cancer.

Plans for an open workshop meeting sponsored by the National Pancreatic Cancer Project are being formulated. This workshop will be held in New Orleans in the spring of 1979.

NATIONAL PANCREATIC CANCER PROJECT

(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
22	$2,588	22	$1,782	44	$4,370

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Description

The ultimate goal of the National Prostatic Cancer Project and, therefore, the focal point toward which all of its efforts are directed, is the prevention of prostatic cancer. This objective is complemented by immediate Project endeavors aimed at decreased morbidity and mortality from this disease. The overall strategy of the National Prostatic Cancer Project for accomplishment of these objectives has been the development of a multidisciplinary, investigator-initiated research program in those areas of clinical and experimental research which offer the opportunity for immediate and visible success. The national plan for prostatic cancer research which has been developed emphasizes earlier disease detection, diagnosis, prognosis, and optimum treatment of all stages of this disease. In order to realize these ends as well as the ultimate goal of prevention, studies directed at the etiology and natural history of the disease have also been implemented.

Current projects receiving support in the areas of detection and diagnosis include studies of histopathologic grading of prostatic carcinoma and establishment of grading criteria useful for discrimination, diagnosis, and prognosis of the different expressions of the disease. A major effort continues to be directed at developing and testing specific and sensitive immunochemical assays for prostatic acid phosphatase as diagnostic tools. In addition, a search for other biochemical and antigenic components which may be specific markers of prostatic cancer at its onset is under way. The establishment of a central resource in the form of a repository for cell cultures, tissues, and serum samples from men with carcinomatous, benign hypertrophic and normal prostates has greatly facilited these and other projects, such as those evaluating the endocrine aspects of prostatic carcinoma and the role of hormone receptors in all aspects of this disease. The National Project is also supporting development and evaluation of transrectal ultrasonography, which is a new noninvasive technique for detecting, staging, and monitoring prostatic responses to therapy.

Treatment of prostatic cancer has been the subject of major interest and endeavor to the National Prostatic Cancer Project starting with clinical cooperative trials initiated in 1973. This is the first nationally randomized study of single chemotherapeutic agents on patients who fail to respond or no longer respond to conventional treatment. These are Stage D patients with histologically confirmed disease and distant metastases. Acid phosphatase, alkaline phosphatase, and the isoenzymes (bone, liver, and others) of alkaline phosphatase in the sera from patients with prostatic cancer admitted to these chemotherapy trials are being measured. Clinical trials using both single agents and combinations of agents, also under way, are aimed at patients with metastatic disease who are stable after previous treatment or who are previously untreated. Trials have also been initiated to determine the efficacy of chemotherapy as adjuvants to surgery or definitive radiotherapy in patients with earlier stages of the disease. The National Project also supports radiotherapy studies comparing extended field treatment--that is, irradiation--to areas of known involvement plus contiguous lymph nodes, with local field treatment involving irradiation limited to known areas of tumor. Control trials directed at determining the specific efficacy of radiotherapy are also under way.

The National Project supports efforts within the treatment area which are directed toward the synthesis of compounds with specific prostate cytotoxicity. Systems developed to test *in vivo* and *in vitro* the efficacy of chemotherapeutic agents include drug inhibition of DNA synthesis in castrated testosterone-stimulated rats and enzyme (5α-reductase, arginase) inhibition in prostates of various nonprimate species and the baboon.

There is a two-pronged approach to ongoing research in the areas of etiology and prevention of prostatic cancer. Advanced methodologies are being used to explore whether prostatic tissue contains molecular genetic material and antigens that are characteristic of mammalian oncogenic viruses. The relation of prostatic carcinoma antigens to cell-mediated immunity and the possibility that cytomegaloviruses may play a transforming and oncogenic role in prostatic cancer are being studied. Investigation of the etiology of prostatic cancer is supported significantly through continuing development of new cell culture and animal tumor models which are available to researchers through the National Project. These models are also in use for screening new chemotherapeutic agents. Other etiologic and epidemiologic studies are probing the relation of dietary, occupational, socioeconomic, sexual, and medical factors to prostatic cancer.

Accomplishments

Cytoplasmic receptors are critical to the action of steroid hormones and several groups have contributed new information on these proteins for the detection, diagnosis, and selection of optimal therapeutic management. Using the potent synthetic androgen, methyltrienolone, high affinity binding characteristic of a receptor was detected in the cytosol of 29 of 30 hypertrophic prostates (Menon, M., et al. 1978). However, this compound also has some characteristics of binding to a progesterone receptor. It was concluded that even though the androgen receptor is not demonstrable in the cytosol of prostates from noncastrated men, it can be measured in nuclear extracts of androgen responsive tissue, where the major influence of a hormone is exerted in a target tissue.

In studies of dihydrotestosterone (DHT) as a biochemical marker for the differentiation of prostatic cancer, DHT interference with receptor binding was found to be a more important determinant of tissue DHT than changes in 5α-reductase of plasma testosterone (T) (Albert, J., et al. 1978). In comparing the differentiation of prostate cancer by histologic grading techniques versus tissue DHT levels (Albert, J., et al. 1978; Chu, T. M. 1977) low grades were associated with tissue levels of DHT greater than 1.8ng/g of tissue, representing biochemically differentiated cancer. Stage D patients with grade 2-3 histology (undifferentiated) and with tissue DHT levels greater than 2.5ng/g had objective regressions, suggesting that the biochemical marker may be more predictive of response to therapy than the histologic grading.

Recently, the presence of both androgen and estrogen receptors was demonstrated in the baboon prostate which, as is also true for the human prostate, is separable into functionally and histochemically different lobes (Karr, J. P., et al. 1978). These investigators also reported that cyproterone acetate and diethylstilbestrol are useful agents in androgen and estrogen receptor studies, and were able to assay androgen and estrogen receptors in gross and needle biopsy specimens of human prostates (Karr, J. P., et al. in press). The percent displacement of labelled estradiol in needle biopsy cytosol binding sites by DES was correlated with the endocrine status and therapeutic management of prostatic cancer patients.

Studies on animal models have characterized the Dunning R3327-H adenocarcinoma which is a transplantable and well differentiated prostate cancer. This is a slow-growing tumor with a tumor doubling time of 17-20 days (Smolev, J. K., et al. 1978; Weismann, R. M., et al. 1977). Approximately 80 percent of the total tumor cells require androgen for maintenance and growth, and 20 percent of the total tumor cells are androgen insensitive. Both the hormone-sensitive and insensitive cells have similar growth rates. The tumor undergoes partial involution with castration, antiandrogens, or estrogen therapy; however, the smaller number of hormone-insensitive cells continue to grow unabated and the tumor relapses to a hormone-insensitive state. A cell line has been developed from these hormone-insensitive cells and this line is being characterized. In related studies, the surprising discovery that the androgen-dependent prostatic tumor model (R3327) does not grow in the rat testicle was reported, implying a toxicity from high androgen concentrations on this tumor. A second line of the Dunning tumor, which is anaplastic and rapidly growing, has been developed as a separate line, R3327-AT. This system is not hormone-sensitive and is not a squamous cell tumor, but appears to be an adenocarcinoma. This anaplastic line is a very rapidly growing tumor with a doubling time of approximately two days. Both the hormone-sensitive and anaplastic tumors have been tested for their ability to respond to chemotherapy and adjuvant therapy. This adjuvant therapy has increased the life span considerably and in some cases produces what appear to be cures. In addition, the effects of castration have been monitored on the hormone-sensitive tumor, and while the tumor relapses, a cure following hormone deprivation has not been obtained. Early rather than late castration is more beneficial on increasing life span in these tumor-bearing animals.

Possible viral involvement in the development of prostatic cancer has been studied and results indicate that in those few patients whose tumors possess a viral-like p30 antigen, the antigen is nonantigenic to the patient (Mickey, D. D., et al., 1977; Webb, K. S., et al., 1977). Attempts to identify viral-like proteins on the surface of, or in, prostate cells using immunochemistry and electron microscopy have produced no indication that C-type RNA viruses play an etiologic role in prostatic cancer (Stone, M. P. et al., 1977). Similar conclusions were drawn from studies of the human prostate tumor line DU-145 which has been heterotransplanted into nude mice (Stone, K. R., et al., in press).

A screening program initiated in about 30 institutions to determine the efficacy of immunochemical assay of prostatic acid phosphatase (Chu, T. M., in press; Chu, T. M., et al., in press Wajsman, Z., et al. 1978) in the early detection of prostatic cancer and in the monitoring of patient progress has undergone preliminary analyses. Results on cancer patients show that the counterimmunoelectrophoresis and radioimmunoassay tests are substantially more sensitive than biochemical methods. Results (Wajsman, Z. in press) of the screening program for early detection are too early to permit the follow-up necessary to fully evaluate the ability to distinguish BPH from early disease. However, the results obtained thus far indicate that prostatic cancer can be detected by these methods in early stages. The specificity of the counterimmunoelectrophoretic method (CIEP) and a radioimmunoassay method (RIA) has been demonstrated in these pilot studies. Furthermore, these very sensitive methods have a potential for early detection of prostatic cancer and its early metastatic spread because of the specificity, reproducibility, and accuracy of these methods.

Over 800 patients have been randomized to eight chemotherapy protocol studies in nine participating institutions throughout the United States. The different protocols are designed to evaluate single and combined chemotherapeutic agents in patients with histologically proven metastatic (Stage D) prostatic cancer (Murphy, G. P. et al., in press; Schmidt, J. D., et al., in press). These protocols are further divided to consider patients who have had prior extensive radiotherapy and cannot be treated with myelosuppressive agents. Based on objective response criteria, 5-FU, Cytoxan, Estracyt, and DTIC have proven effective and have increased survival time. Additional studies are in progress to treat clinically stable Stage D patients and newly diagnosed Stage D patients with combinations of hormonal and chemotherapeutic agents. Early results suggest that the combination of DES and cytoxan may be acting to prevent or delay progression of disease in both newly diagnosed and stable Stage D patients.

Other Program Activities

The need for a reliable, reproducible histologic grading system that will result in improved diagnosis, prognosis, and survival estimates; selection of optimal therapy; and evaluation of response to therapy for prostate cancer patients is well recognized. To address this need the National Prostatic Cancer Project sponsored four small conferences on "Histological Grading of Prostatic Cancer."

On June 6-7, 1978, a Workshop was held at Roswell Park Memorial Institute to bring together the participants of the four "mini-conferences" and other pathologists and clinicians for the exchange of views and a search for commonality among the grading systems currently in use. A grading system may evolve with potential universal acceptance.

The National Project has sponsored the publication of Prostate Cancer Today, Editor, Gerald P. Murphy, M.D., D.Sc. (in press). This publication with contributions from the Working Cadre provides a comprehensive multidisciplinary overview of prostatic cancer. With the American Cancer Society, the National Project is field testing new radioimmunoassay and immunochemical methods, developed by Project grantees for directly measuring prostatic and acid phosphatase. These methods have potential for early detection of prostatic cancer. This program is coordinated, monitored, and evaluated by the National Prostatic Cancer Project.

Emphases and Projections

The National Prostatic Cancer Project will follow the pattern of pursuing the approved National Plan insofar as current knowledge allows. Characterization of hormone receptors in normal, BPH, and cancerous prostatic tissue will continue in several laboratories. Improved methodology and new approaches developed by the National Project grantees, including measurement of subcellular fractions for hormone and receptor concentrations and the use of new agents with high specificity for receptors, should result in assays that predict which prostatic cancer patients may benefit from hormonal minipulation, including orchiectomy. Microtechniques for assay of 50-100 mg of biopsy tissue have already been applied.

Transrectal ultrasonography will be further tested as a noninvasive technique for detecting prostatic cancer and monitoring therapeutic response. The limitations are being further delineated since this method appears to be valuable in staging the disease, and is useful in evaluating patients with prostatic nodules or negative biopsy findings.

Several investigators have been successful in growing prostatic tissue in culture systems. Studies in progress will further characterize the environment necessary for epithelial cell growth. In addition, identification of positive markers for prostatic epithelial cells will be sought through studies of enzyme distributions and concentrations (5α-reductase, arginase, acid, and alkaline phosphatase), zinc uptake, and citrate metabolism. Human and animal prostate tumor immunology and virology studies will also focus on identification of specific markers for prostate cancer cells such as isoenzymes (lactic dihydrogenase) and polyamines.

Animal and in vitro tumor models will be used to test new chemotherapeutic agents and to further characterize the biological natural history of prostatic cancer. In addition, there are numerous other ongoing and expanded investigations which have been approved, including: epidemiologic studies in search of causative risk and genetic factors in the development of prostatic cancer, hormonal dependence of prostatic cancer, measurement of serum prolactin levels, histologic grading, evaluation of intrinsic and extrinsic factors which determine the malignant character of prostatic cancer, measurement of trace metals in prostatic cancer, studies of the surface of normal and malignant prostatic cells, and study of immunoregulation of prostatic cancer. Clinical and treatment investigations will include, investigations of lymph node spread in prostatic carcinoma, use of combination cytotoxic chemotherapy of Stage D cancer of the prostate, use of adjuvant chemotherapy for carcinoma of the prostate in patients with positive pelvic or para-aortic lymph nodes, evaluation of elective radiotherapy of axial skeleton in patients with Stage C carcinoma of the prostate, and evaluation of treatment modalities and study of factors that potentiate tumors in animal models of prostatic adenocarcinoma.

The cooperative clinical trials section of the National Project has been conducting Phase II trials to determine the efficacy of single and combination treatments of hormone and antitumor agents in patients with advanced disease. These trials have demonstrated promising activity for several agents and now Phase III trails have been initiated to evaluate two agents when used as adjuvants to definitive prostatectomy or cryosurgery or to definitive radiotherapy. These Phase III trials are the first to use adjuvant chemotherapy against early stages of prostatic cancer.

NATIONAL PROSTATIC CANCER PROJECT

(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
31	$2,676	17	$1,640	48	$4,316

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CLINICAL ONCOLOGY PROGRAM

Description

The Clinical Oncology Program encompasses a wide range of research activities aimed at the treatment and control of malignant disorders. While trials of new anticancer agents, either singly or in combination, constitute a large portion of this research, other approaches to treatment are also under investigation. These include modifications of surgical procedures, the manipulation of hormones in the treatment of hormone-dependent malignancies, and hyperthermia. The Program also supports research efforts to identify biochemical and genetic markers which can predict the response of a tumor to therapy or monitor the efficacy of treatment, and the development of animal and computer models of human malignancies to assess the effects of drugs. Innovative methods of delivering antitumor agents more directly to the tumor site are under investigation.

Supportive care of the patient undergoing cancer therapy is another important objective, including studies in nutrition, the reduction of toxic effects of drugs, and the prevention and detection of infectious diseases in the patient compromised by cancer or its treatment. The Program also includes studies on the relationship and control of conditions which often accompany malignancy such as hypercoagulability and hypercalcemia. Investigations of premalignant disorders and late appearing effects of cancer treatment on the surviving patient are also encouraged.

Research endeavors in clinical oncology are supported by either of two mechanisms--the traditional single-project grant, which focuses on a selected research topic, or the program project grant, which unites a number of investigators in the same institution in studying related aspects of a common problem. In the latter case, efforts may range from clinical trials of chemotherapy regimens to the development of new agents and the study of their pharmacological properties in both animals and humans. These program projects often include basic laboratory research on the nature and growth of cancerous cells, diagnosis and monitoring of tumors, and the total care of the patient under treatment. The subject of the program project may be a single tumor type or group (e.g. breast, brain, pediatric tumors) or cover a wide spectrum of malignancies.

Achievements

During the current year, the Clinical Oncology Program has supported 82 randomized chemotherapy clinical trials, including 28 projects dealing with hematological tumors and 54 projects on adjuvant chemotherapy of solid tumors. Three projects involving purely surgical trials were funded, as well as three projects investigating immunotherapy. In addition to these randomized clinical trials, 23 projects involving Phase I or Phase II studies were supported.

The ability to predict from laboratory tests how a malignant disease will respond to a given treatment before subjecting a patient to potentially dangerous or inappropriate therapy has been the subject of research by a number of investigators. Rustum and Preisler, (1977) have shown that the uptake and retention of cytosine arabinoside (Ara-C) by leukemic blast cells in vitro is prognostic of the response of a patient with acute myelocytic leukemia (AML) to this therapy. The correlation of the pretreatment drug sensitivity test and patient response has been so significant that this group has abandoned the use of Ara-C in patients whose cells showed poor uptake and retention of this drug.

McCaffrey and co-workers have found that leukemias can be classified into therapeutically significant groups by the presence of a biochemical marker, terminal deoxyribonucleotide transferase (TDT), in their blood cells. TDT is typically found in lymphoblasts and is characteristic of acute lymphoblastic leukemia (ALL). In patients with blastic crisis of chronic myelogenous leukemia (CML), whose cells contained TDT, an excellent response rate was achieved by the usual treatment for ALL, vincristine and prednisone, while those without TDT did not respond well (Fosburg et al, 1977). Clarkson's group also reports that 20 to 30 percent of patients with blastic CML have a lymphoblastic transformation as determined by TDT and N-alkaline phosphatase markers and will respond to a vincristine and prednisone regimen (Arlin et al, 1977).

In a similar vein, laboratory methods of detecting a relapse or progression of disease before clinical signs are apparent have been sought. If this were possible, therapy would be initiated before a critical stage is reached. Hittelman and Rao, (1977) have sequentially followed the proliferative potential of bone marrow cells from leukemia patients in clinical remission by the premature chromosome condensation technique. Among patients in whom an abrupt and significant change in proliferative potential occurred, 11 of 12 showed clinical symptoms of relapse within approximately three months. Spitzer, et al, (1977) have demonstrated that changes in pattern of growth of bone marrow cells in culture from patients with preleukemic disorders are both diagnostic and prognostic of progression to a malignant state before it can be detected by the microscopic appearance of the cells.

Bone marrow transplantation has been considered a desperate last effort to save acute leukemia patients who have failed all conventional therapy. This procedure involves killing virtually all the blood-forming cells of the patient by radiation and intensive chemotherapy and then introducing bone marrow cells from a tissue-matched sibling in hopes of repopulating the system with nondiseased cells. Although many problems involving the susceptibility of the patient to infection while awaiting reconstitution of his blood system and the possibility of rejection of the graft or graft-versus-host disease remain, Thomas (1977) reports that a significant number of patients can achieve long-term remission or even "cure" of their disease by bone marrow transplantation. He feels that many of the failures are a direct result of the critical condition of the patient at the time transplantation is attempted and argues that the technique has now developed to a point where its efficacy should be tested earlier in the course of the disease.

Storb, et al, (1977) studied retrospectively the prognostic factors for survival and absence of graft versus host disease in 77 bone marrow transplanted patients with aplastic anemia. Of 24 factors analyzed, only two were found to correlate well with a favorable prognosis, i.e., (1) sex match of donor and recipient, and (2) the absence of refractoriness to random donor platelets at the time of transplantation.

The technology developed over recent years, which allows the proliferation and differentiation of blood-forming cells in the laboratory, has led to a rapid increase in knowledge of the mechanisms by which blood cell proliferation is normally regulated and of what happens to these controls in malignant blood diseases.

A radioimmunoassay for colony-stimulating factor (CSF), a regulator of white blood cell production, has been developed by Shadduck and Waheed (1977). Antibodies to CSF which inhibit white blood cell proliferation have also been produced (Shadduck, et al, in press). These methods of study will allow further investigation of abnormal white cell production in the leukemias.

Normal polymorphonuclear cells (PMN), a type of white blood cell, have inhibiting activity upon the number of bone marrow cells which will spontaneously proliferate in culture thus producing a steady state of white cell numbers in the normal individual. In 58 patients with chronic myelogenous leukemia (CML), a quantitative difference was found in the inhibiting activity of PMN's. Target bone marrow cells of CML were also found to be less sensitive than normal cells to the inhibitor produced by PMN's. These factors may help explain the selective advantage of leukemia cells over normal cells.

The presence of cytoplasmic estrogen receptors in human breast cancer has proven to be prognostic of the tumor's response to endocrine therapy in approximately two-thirds of tumors which are receptor-positive. The reason for this heterogeneity of response has been approached in several studies. Straus's group (1978) analyzed 30 patients determining estrogen receptor content and labeling index from separate areas of tumor tissue in separate lesions from the same patient. In over 30 percent of the patients studied, both clear negative and clear positive receptor values were obtained suggesting a heterogeneity of tumor within the same patient.

An important research emphasis has been the development of means of "rescuing" normal tissues from the toxic effects of antitumor agents so that higher doses of these drugs may be administered without danger to the host. Frei's group (1977) has found that thymidine is a potent rescue agent for high-dose methotrexate treatment, resulting in a more rapid reversal of bone marrow suppression than when leucovorin is used as a rescue agent.

Emphases and Projections

While great progress has been made in the treatment of hematological malignancies in recent years, especially lymphoma and childhood leukemias, the major treatment for solid tumors is still surgery. Chemotherapy and immunotherapy for control of these tumors after surgery, or for inoperable tumors, remain important areas for future study. Alternate methods to chemotherapy such as the manipulation of hormones and hyperthermia will also be actively encouraged.

The effects of nutrition on the patient undergoing treatment are still under investigation, and new methods of delivering nutrients and of adjusting the contents to the best advantage of the patient must be sought. Premalignant disorders also deserve vigorous investigation so that they may be controlled before they become frankly neoplastic. The long-term effects of cancer therapy upon the controlled or cured patient must be carefully evaluated, and methods of protecting the patient from potentially lethal or disabling complications of therapy should be developed.

CLINICAL ONCOLOGY PROGRAM

(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	No.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
TRADITIONAL	53	$ 4,560	25	$2,096	78	$ 6,656
PROGRAM PROJECTS	21	12,970	10	7,793	31	20,763
CONFERENCES	0	0	1	9	1	9
TOTAL	74	$17,530	36	$9,898	110	$27,428

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CANCER DIAGNOSTIC RESEARCH AND PREVENTION PROGRAM

Description

The Diagnostic Research and Prevention Program is primarily involved in research related to prevention, early detection, and diagnosis of cancer, and research on the application of such knowledge to populations at risk. The program supports research directed towards the improvement of currently existing techniques as well as the development of new detection procedures and diagnostic modalities. This includes the development of new sensitive and simple-to-use testing procedures for identifying populations at high risk to cancer. The program also includes research on early detection of predisposing factors and on factors associated with environmental, occupational, behavioral, and life style habits which contribute to the exposure of agents hazardous to human health. The improvement and evaluation of known diagnostic procedures by application to selected subgroups in high-risk populations is supported as is the utilization of current leads in the field of biological science, instrumentation, and computer technology to assist in the development of new diagnostic procedures. Particularly important in this area is the development of non-invasive diagnostic methods.

Research Accomplishments

Ceriani, et al, (1977) showed that cell-type specific antigens associated with plasma membrane were found in mammary gland and liver. Mouse mammary epithelial (MME) cell antigens were found to be cell-type specific, and were shown to be retained, to a large extent, by mouse mammary epithelial cells after neoplastic transformation. These MME antigens were expressed in mammary tumors of the several strains tested and were not expressed in tumors whose normal counterpart was other than mammary tissue. They were not dependent on cell culture conditions or the presence of murine mammary tumor virus, and therefore, they could be used as an ubiquitous cell type marker for mouse mammary epithelial cells in both normal and neoplastic cells. The expression of MME antigens was lower in neoplastic than in normal mouse mammary epithelial cells. Evidence from cross-absorption experiments demonstrated that the antigenic difference between normal and tumor cells was probably due to a deletion of one or more of the antigenic components from the neoplastic cells. The preparation and characterization of MME antigens from the mouse milk fat globule (MMFG) were described. Antisera prepared in rabbits against fat-free MMFG material identify cell-type-specific MME antigens on the surface of mouse mammary epithelial cells and of mouse milk fat globules. Anti-MME did not bind to cells from other mouse tissues. Specificity of anti-MME for MME antigens on the MMFG was demonstrated by competition in a radioimmunoassay and by cross-absorption experiments. Further, purification of the antisera and identification of specific MME antigens is under way.

Using a mail survey, Shore and his colleagues (1977) have studied breast cancer in 571 of 606 women treated with x-rays for acute postpartum mastitis. The incidence of neoplasms was compared with that of three nonirradiated control groups--nonirradiated sisters of the treated women; women with acute postpartum mastitis not treated with x-rays; and the nonirradiated sisters of the latter group. In the irradiated group, with a mean dose of 247 rads to both breasts, the overall relative risk of breast cancer was 2.2 for years 10 to 34 postirradiation and 3.6 for years 20-34. The dose response for malignant and benign breast neoplasms was compatible with a linear fit. When the doses were comparable, fractionation of exposure did not reduce carcinogenic action. Women over the age of 30 at radiation had as great an excess risk of breast cancer as did younger treated women. The overall risk of developing breast cancer was approximately 8 to 10 cases per million per rad per year, an increase of 0.5 percent per rad. This study presents evidence that breast irradiation confers a breast cancer risk that cannot be accounted for by genetic factors or by an existing disease state. Neither can it be accounted for by other known risk factors for breast cancer which were measured in this study. Although early first pregnancy confers a degree of protection against cancer in general, there was no evidence it protected against radiation-induced breast cancer. For those women first pregnant before age 30 years, the relative risk was 3.6, whereas, in the remainder of the study group the relative risk was 1.7. The absolute excess risk was approximately equal for these two groups. The causal relationship between radiation and breast cancer is further supported by the dose-response relationship and by the fact that an excess of breast cancer was found only in irradiated breasts among women given unilateral radiation.

A three-year study on the early radiologic detection of lung cancer revealed that 15 percent of diagnostic radiology errors were of omission (Kundel, et al, 1977). Parallel studies showed that the majority of tumors were detected but that they were not recognized as tumors or were given a very low probability of being tumors and were disregarded. Improved human performance in diagnostic radiology was attempted by modifying the display of the image to make tumors more visible or by modifying the search of the film reader. At this stage, it was demonstrated that the television-image intensifier system, in combination with a video disc recorder with extensively modified electronic circuitry, can accomplish three objectives. It has acceptable drift stability, it can produce images that can be aligned with each other to the required tolerances, and it can be compensated for a wide range of density variations between images. The remaining problem was in the signal to noise ratio of the vidicon camera signal. They have recently obtained a Recticon MC510D camera containing a 32x32 matrix of photodiodes with appropriate optics and electronic scanning. To date, they have had a mount constructed so that the camera can be positioned onto the image intensifier tube and view the fluoroscopic image through the cine port. They have designed and built a device for controlling the frame rate of the scanning. The frame rate is now synchronized to the line frequency. Preliminary measurements which have just been completed, have provided a five-to-ten fold increase in intensity resolution. Furthermore, the video signal can now be entered into the LINC-8 computer on line and they are now optimistic that pulmonary pulsations will be able to be accurately measured. A program was designed to study the manipulation of the observer's search to improve detection. The first two years were devoted to hardware and software development of a system to record the fixation pattern of an observer viewing a film, to analyze the location of fixations, and to feed back information about where the eye has or has not fixated so that a more thorough search can be carried on. The entire process of data collection and feedback was required to take place on line in real time. Eye fixation data were collected using infrared sensors attached to a pair of eye glasses. The sensors are interfaced to a PDP 11/40 computer, and programs have been written to do a long list of tasks. The display that has been designed and is currently being tested consists of a 14 x 16 matrix of one inch square conductors, each individually controlled by the computer to permit the illumination of any cell or pattern of cells in the matrix that is superimposed over the radiograph being viewed. The display is controlled by a single 16-bit word, hard-wired from the computer through a decoder which splits the word into strobe and template pulses, a latch memory which eliminates the necessity of refreshing the display except to introduce changes, and reed relays which are used as drivers for each cell. Thirty-two 16-bit machine language commands can completely change the entire display. A shutter is introduced at the light source for tachistoscopic presentation and is controlled by the computer. Both the equipment and the computer software are presently furnishing data which are being evaluated.

The toxonomic intracellular analytic system (TICAS) has been established for accurately classifying individual normal and abnormal cells in routine Papanicolaou stained cervical cytology smears by processing cell image data obtained from a scanning microscope (Koss, et al, 1977). The TICAS system has been applied quite successfully to diagnostic bladder cytology, and work on lung cytology is under study. Data obtained from these latter studies are being processed and analyzed by program sequences from the TICAS on a CDC 6400 computer for cell classification. Recently, they have added capability for optical density measurements at three wave lengths. This string of digitized optical density values is acquired by a computer and used for cell classification. A self-learning program guides the computer in extracting cell features from the data, selecting useful features, assigning weight to these features, and deriving classification rules. Initially, data from cells classified by a cytopathologist constitute a learning set from which the computer-generated classification criteria are derived. From these criteria, objective diagnostic standards are established for automated diagnostic recognition of cells in appropriate cytologic samples.

Ultrasound mammography is a safe, noninvasive, painless method of producing high-resolution tomographic sections through the breast. In other tissues which also have a high fat content, e.g., the orbit, diagnostic accuracies of greater than 95 percent have been achieved. Ultrasound may be able to demonstrate very small lesions which escape radiographic detection. During the past two years, efforts to refine ultrasonic diagnostic equipment and criteria for the detection of breast cancer and to develop algorithms for digital analysis of acoustic textures of tissues have been encouraging (Baum, 1977). The results from the first series of patients on this project were attained on a system which had not been completed; however, following this series, the instrumentation was integrated and the technology was further developed. Currently, ultrasound mammography is being performed in a random fashion without prior knowledge of other diagnostic steps. High resolution equipment which displays changes in acoustic properties of the tissues and which may be recorded is being used. On a small group of women, the rate of agreement between ultrasound and the pathological diagnosis was very good (88 percent), while false negatives were a minimum (5 percent). Additional clinical data are being accumulated. Special equipment such as a fast digitizer will enable them to digitize both R. F. and video ultrasound and to analyze the data.

Studies on the pathobiochemistry of melanoma are beginning to establish the outline for the biochemical pathways involved in pigmentary and nonpigmentary metabolism in malignant melanoma. An automated chromatography system for detecting catecholamines was successfully developed (Banda, et al, 1976). The system separates and detects the "acidic" metabolites of DOPA. The "basic," decarboxylated DOPA metabolites, will not elute from the cation-exchange resin in this system. The automatic analysis system using the anion-exchange resin coupled with DPPH detection which was developed last year is currently being used to screen melanoma urines for abnormalities in catecholamine metabolism (Banda, et al, 1977). The analysis takes but one hour, and does not require prior extraction of the catecholamines from urine. During this year, emphasis has been given to identification of the unknown chromatographic peaks, in assigning quantitative levels for the excretion of the various DOPA metabolites as well as pursuing refinement of the chromatographic techniques.

The quantitative measurement of the thyroglobulin in unextracted human serum has been shown to be a sensitive indicator of thyroid malignancy and the metastases of some of the tumors. It has previously been shown (Van Herle, et al, 1976) to be a simple and inexpensive way to evaluate the presence of the development of metastatic disease in cases of established differentiated thyroid malignancies. The procedure has been successfully used as an index to cure and reactivation of the disease process. Studies to further improve the specificity of the procedure as a diagnostic test for thyroid cancer are continuing.

A serum protein fraction salted out by ammonium sulfate fractionation at 50-60 percent saturation was found to be evaluated for tyrosinase activity and specific electrophoretic tyrosinase patterns in several malignant diseases (Chen, et al, 1977). Endogenous tyrosinase inhibitors were present in such enzyme preparations in certain diseases. The ultrafiltration of the supernatant separated from the serum tyrosinase fraction yielded four fractions of tyrosinase inhibitors with high molecular weights and two fractions of tyrosinase activators with low molecular weights. These factors appeared characteristically different in certain diseases. A number of studies have revealed a relationship between some serum enzymes and tumor growth. These include alkaline phosphatase in bronchogenic carcinoma and leucine aminopeptidase in disseminated malignant disease. Determining the relationships of these is of clinical importance for specific biochemical diagnosis and evaluation of malignant disease.

As a result of the above data, serum tyrosinase was studied in 49 malignant diseases plus miscellaneous sarcomas (Chen, et al, 1978). Serum tyrosinase activity observed in diseased people ranged from 1.5 to 4.5 times higher than in normals. Several of the highest values approached those found in melanoma and breast carcinoma previously reported. The electrophoretic patterns of serum tyrosinase melanin bands defined as sets of R_f value were different from disease to disease. Three tyrosinase inhibitors contained in the serum tyrosinase preparation in many diseases were demonstrated as colorless wide bands on the gel after electrophoresis of the enzyme preparation and incubation with L-dopa.

Davidsohn and his colleagues (1977) studied carcinomas of the skin, gallbladder, breast, and cervix which contain the A, B, and H antigens. In the urinary bladder they found the loss of iso-antigens was related to the degree of the morphologic dedifferentiation of the carcinomas. These results were identical with their previously reported findings in carcinomas of other organs, namely, that the loss of the antigens was related to the degree of anaplasia and that it usually precedes the formation of metastases. In the cervical cases, grades I and II showed the largest number of positively reacting carcinomas with the RCA test. To date, not enough data are present with the RCA test to warrant significant conclusions for normal and carcinoma tissues from the gallbladder, breast, foreskin, and basal cells.

Other Program Activites

A conference grant was awarded to the American College of Radiology for partial support for 100 resident physicians to participate in a workshop on detection, diagnosis, treatment, and management of patients with breast cancer. The American Cancer Society sponsored 35 fellows plus 15 radiation residents. The scientists who participated in the five-day workshop were specialists in surgery, pathology, radiology, diagnosis, treatment, and rehabilitation. The results of the five-day workshop had an impact on the young physicians as measured by a questionnaire. The technology transfer that began during the lectures, demonstrations, and discussions will affect other residents and community physicians during the year. In the past, these meetings have had a far-reaching impact on residents and community physicians.

Emphases and Projections

During the past fifty years, thousands of new chemicals have been introduced into our environment. Many of these compounds have been demonstrated to produce undesirable changes in the physical, chemical, and/or biological characteristics of the air, soil, and water around us. These changes may alter our life styles and produce certain effects which are hazardous to our health. Numerous chemical compounds are carcinogenic in animals and man. Populations exposed to these new materials derived from technological changes often have a high cancer risk. In view of the increased risk of malignant disease that the environmental pollutants may produce, emphasis is being given to innovative research to develop new cancer diagnostic procedures. A number of basic research projects are under way whose goals are to develop better methods for the detection and definitive diagnosis of cancer at an early stage so that treatment has a better chance of success. An objective of the program during the coming year is to stimulate other basic research projects for developing and evaluating new procedures for the detection of precancerous changes and very early malignancies. The fields of biological sciences, instrumentation, and computer technology will be stressed in this effort.

CANCER DIAGNOSTIC RESEARCH AND PREVENTION PROGRAM

(DOLLARS IN THOUSANDS)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
TRADITIONAL	22	$2,040	23	$1,802	45	$3,842
PROGRAM PROJECTS	0	0	1	95	1	95
YOUNG INVESTIGATOR AWARDS	0	0	2	66	2	66
TOTAL	22	$2,040	26	$1,963	48	$4,003

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DRUG DEVELOPMENT AND PHARMACOLOGY PROGRAM

Description

The Drug Development and Pharmacology Program concerns the search for effective agents which act specifically or selectively in the control of cancer. Scientific direction and encouragement are given to investigators in diverse scientific disciplines to pursue research in the chemical, pharmacological, and cytological aspects of abnormal and normal growth processes. Preclinical and clinical research is coordinated and implemented through various stages of drug development. Component areas involve: (1) synthesis of potential anticancer agents through synthetic chemical processes or by isolation from microbial, plant, or animal sources; (2) experimental therapeutics involving screening tests for anticancer activity and toxicologic and other pharmacologic studies; (3) biochemical mechanisms of action which include physiological disposition and drug metabolism, biotransformations, and the mode of action relating to antitumor and pharmacologic response; and (4) pharmacology including the correlation of preclinical and clinical data and experimental therapeutic investigations in man through controlled clinical trials. All research activities in the Drug Development and Pharmacology Program relate to the preclinical Treatment Research thrust.

The concept of drug development involves the exploration of new approaches leading to the development of more effective cancer therapy through the integrated yet diverse contributions of many investigators. In addition to the synthesis of new compounds and the preclinical pharmacology of compounds of interest, fundamental studies on the biochemical and pharmacological basis for selective cellular effects of drugs are carried out by investigators in a variety of experimental systems and in humans. These studies provide important sources of information leading to the design of new drugs with improved selectivity of action. Biochemical and pharmacological studies included investigations on the changes in the regulation of cell metabolism involved in drug biotransformation, cell membrane function, and control of oncogenic transformation, as well as studies on drug dispostion, on qualitative and quantitative differences in drug toxicity to tumor and normal cells, and on pharmacokinetic factors leading to the design of optimal combination in schedules of treatment. The development of new anticancer drugs and new forms of treatment is integrated closely with both basic progress in the biochemical pharmacology of anticancer drugs and fundamental studies on the regulation of cell metabolism. Interactions among these approaches using both preclinical systems and human materials provide an optimal basis for formulation of new ideas leading to advances in the therapy of cancer.

Accomplishments

Synthesis: The concept of bioreductive alkylation is of major significance as a mechanism of action of many naturally occurring and synthetic anticancer compounds. It permits examination of known compounds for the key structural features that may be responsible for their biological activity. By designing inactive forms which become activated only subsequent to an *in vivo* transformation, a mechanistic probe for investigating problems of drug action is established. Predictions regarding structural features of a potentially active molecule can be made. These findings serve as critical guideposts for synthetic programs which have as their objective the construction of compounds with superior biological activity.

A research project (Moore, 1977) uses four relatively simple models to catalog potential bioreductive alkylating agents. On the basis of these models and previously established data, predictions are being made and tested which should lead to production of a series of compounds for cancer screening which ultimately may result in more effective anticancer therapeutic agents.

One example of the application of bioreductive alkylation may be seen with adriamycin. Adriamycin probably has a wider spectrum of clinical activity than any known cancer compound. Clinical evaluations have shown it to have significant activity against various tumors including leukemia, lung cancer, breast cancer, sarcoma, lymphoma, and neuroblastoma. As isolated, adriamycin is a hydroquinone, which in terms of the bioreductive alkylation concept is the penultimate precursor to the quinone methide. Adriamycin has structural similarities to a number of naturally occurring and biologically active naphthazirins whose mode of action could also be one of bioreductive quinone methide formation. From a structural point of view, these compounds are capable of functioning as bioreductive alkylating agents and thus exhibit cytotoxic properties. The significance of the principle of bioreductive alkylation is that it provides a mechanistic rationale for synthesis of compounds which help eliminate the element of chance in the search for more useful anticancer agents.

The nitrosourea compounds are an important class of antitumor agents with demonstrated activity in a broad spectrum of malignant tumors in the human. However, all clinically available agents, with the exception of streptozotocin, induce profound cumulative bone marrow depression. This myelosuppressive toxicity significantly limits the clinical usefulness of these agents. Previous laboratory evidence suggested that carbamoylation might play a major role in the bone marrow toxicity of nitrosourea antitumor agents. This possibility was suggested by the observation that steptozotocin, a methylnitrosourea with negligible carbamoylating activity, is also nonmyelosuppressive.

The results of a recent study (Panasci, et al., 1977) suggest a much more modest role for carbamoylation as a mediator of nitrosourea bone marrow toxicity and lethality. In addition, the present study confirms that *in vitro* carbamoylating activity does not necessarily correlate with antitumor activity. Since carbamoylation did not appear to correlate with any biological parameters investigated, further studies on alkylation were performed. The *in vitro* colorimetric alkylating activities of these nitrosoureas do correlate with antitumor activity. Data obtained in these assay systems support a correlation between alkylation and antitumor activity. The results indicate that increased alkylating activity is responsible for greater myelotoxicity, while four sugar-containing methylnitrosoureas (streptozotocin, epistreptozotocin, 3 -D-glucopyranosyl-1-methyl-1-nitrosourea, 3 -D-galactopyranosyl-1-methyl-1-nitrosourea) result in a reduction of bone marrow toxicity. It is possible that analogs of sugar-containing chloroethyl-nitrosoureas could be synthesized that would lack myelotoxicity and result in a significant enhancement of clinical usefulness of the nitrosourea class of antitumor agents.

Selective Toxicity: The toxicity of most anticancer drugs to the rapidly proliferating cells of bone marrow, intestinal epithelium, and lymph nodes represents one of the major problems in clinical cancer chemotherapy. The use of toxicity-alleviating agents constitutes an important approach in cancer chemotherapy. The objective in this crucial area of research is to reduce this toxicity, without reducing therapeutic effectiveness of the drug.

In one study, using anticancer agents in cell culture, normal cells have been protected from the cytotoxicity of these drugs. (Pardee, et al., 1978). Based on the hypothesis that rapidly proliferating normal cells *in vivo* can also be reversibly shifted into a quiescent state by treatment with protective drugs, and that tumor cells *in vivo* will not be similarly affected, studies were performed to determine relevant effects of cycloleucine *in vivo*. Mice were injected with varying dosages of cycloleucine followed 24 hours later with an anticancer drug treatment. When cycloleucine dosages 100 mg/kg or greater were used, valine was given following the anticancer drug treatment. Results indicate that pretreatment with an appropriate dose of cycloleucine can shift LD_{50} of an anticancer drug given alone to an LD_{10}.

Patients receiving adriamycin have shown an unusually high incidence of cardiac toxicity. In one study, (Vick, et al., 1978), carnitine, a trimethylbetaine analog obtained from meat extract, was shown to protect the isolated Langendorff heart against the cardiac toxicity of adriamycin. It was also shown that carnitine did not interfere with the cytotoxic capability of adriamycin. Although studies in tumor-bearing animals are not yet complete, present data suggest that carnitine may be a valuable adjunct to current chemotherapeutic regimens such as adriamycin. Follow-up studies are in progress.

Predictive Tests: Predictability of individual responses remains uncertain for each of the drugs used against metastatic breast cancer. In one study (Ferguson and Harper, 1977) investigators describe results of using cesium-131 to predict responses of patients treated for metastatic mammary cancer. Cesium-131 was administered intravenously to 39 patients with superficial metastases of mammary carcinoma and the concentration in tumor was compared with that in normal tissue by application of a detector *in vivo*, before and after one to five days of chemotherapy with cyclophosphamide, 5-flourouracil, or diethylstilbestrol. A change of the cesium concentration ratio (tumor/normal tissue) greater than 15 percent after brief treatment correctly predicted the therapeutic effect after one to 39 months on the tumors that were tested in 30 of 33 tests.

The mechanism by which chemotherapy changes the capacity of a tumor to concentrate cesium is not known. Although the technique has proved valuable, the mechanism underlying the increased capacity to concentrate cesium observed in some tumors in response to anticancer treatment has not been explained.

Use of cesium-131 for predictive tests is considered to be without harmful effects. In an extensive study involving tests in 154 patients, no adverse reaction was observed. The low energy of radiation from cesium-131 has the effect of lowering unwanted background counts from tissues surrounding the one being tested, and reducing the need for collimation. The cesium test reliably predicts a strong response to cyclophosphamide, 5-fluorouracil, or diethylstilbestrol thus studied, identifying the minority of patients who will respond unusually well to one drug.

Resistance and Susceptibility: Studies on biochemical and pharmacokinetic aspects of resistance and susceptibility are of importance in defining the mechanism of resistance to tumor cells to cancer chemotherapeutic agents.

During the past year a research group (Alt, et al., 1978), working on the molecular mechanisms of development of resistance to methotrexate in cells in culture has found that cells that have increased capacity for synthesis of dihydrofolate reductase have increased content of specific mRNA, and increased numbers of genes for dihyrofolate reductase. The number of gene copies is exactly proportional to the elevated levels of dihydrofolate reductase. An intriguing property of the cell lines used is that some of them, for instance the S-180, lose high drug resistance, enzyme levels, and gene number when grown in the absence of the drug. Others, the lymphoma-derived L-1210-resistant cells are stable resistant in the absence of methotrexate. After growing resistant S-180 cells in the presence of high methotrexate concentrations for two years, they also become stable and with high enzyme and gene copy number. Progress is being made to enable understanding of how tumors resist anticancer agents. Planning of rational and effective drug protocols for clinical treatment of tumors may be achieved through precise understanding of the mechanisms of resistance.

Biochemical Mechanisms of Anticancer Drugs: It is important to establish the biochemical mechanisms involved in the degradation of DNA by clinically effective antitumor drugs. Bleomycin is being used to study this mechanism in mammalian cells (Chein, et al., 1977). The significance of establishing a precise molecular basis for the fragmentation of DNA induced by antitumor agents is that observations may be applicable to other antitumor agents that degrade DNA. As more compounds of varied chemical structure are demonstrated to degrade DNA, it will be possible to establish structure activity relationship for compounds of this type.

A persistent problem in understanding the mechanism of bleomycin action had been the role of 2-mercaptoethanol and other organic reducing agents in promoting the drug's effect on DNA. Since bleomycin was first isolated as a copper chelate, the possibility occurred that adventitious trace metals in the reaction medium would be reduced by organic reducing agents. Metal ion oxidation in an aerobic atmosphere in the presence of bleomycin and DNA could then be instrumental in DNA degradation.

In examining the interaction between bleomycin and low concentrations of Fe(II) in the degradation of DNA it was found that complete conversion of simian virus 40 DNA to acid-soluble products occurs at approximately equimolar levels of Fe(II), bleomycin, and DNA. Fe(III) does not substitute for Fe(II) in this reaction. Optical spectral studies revealed that an oxygen-labile complex was formed between bleomycin and Fe(II). The novelty of these experiments lies in the specific interaction of bleomycin and Fe(II) in causing extensive degradation of DNA in the absence of organic reducing agents. Studies are continuing which will help to clarify the critical role of trace metals in relation to the activity of the drug and DNA degradation.

α-(N)-Heterocyclic carboxaldehyde-thiosemicarbazones have been shown to be potent inhibitors of the biosynthesis of DNA in mammalian cells (Agrawal, et al., 1977). Studies with transplanted murine neoplasms have demonstrated that the enzymatic state responsible for the blockade of DNA replication is at the level of ribonucleoside dephosphate reductase, an enzyme of critical importance for the generation of the deoxynucleoside triphosphate precursors of these macromolecules. Kinetic studies were carried out with a partially purified enzyme from a rat tumor in an effort to define the molecular mechanism by which agents of this class inhibit the activity of ribonucleoside diphosphate reductase. Results were employed to design 4-methyl-5-amino-1-formyl-isoquinoline (MAIQ-1), a derivative of this class with strong inhibitory potency for ribonucleoside diphosphate reductase, as well as the other necessary requisite properties for clinical trial as an antineoplastic agent.

Targeted Cancer Chemotherapy: The targeting and delivery of anticancer drugs to certain anatomic and specific target cells is an area of current interest. Biodegradable, encapsulation carriers have the potential to target a wide variety of anticancer agents, thus reducing tumor-host imbalance by altering the distribution, uptake, or effects of drugs so that tumor cells might be damaged substantially more than normal cells. Ideally, a carrier for targeting of intravascularly administered anticancer agents should restrict the distribution of the drug to the desired target area, deliver the drug preferentially to tumor cells, provide a controllable and predictable rate of drug release, and undergo biodegradation, with prompt elimination and minimal toxicity of the breakdown products.

A new drug delivery vehicle has been developed for the localization of intravascularly administered, water-soluble, chemotherapeutic agents at specific target sites (Widder, et al., 1978). Studies in mice revealed no overt toxic effects of the carrier. The drug carrier consists of albumin microspheres in which magnetically responsive, ultrafine Fe_3O_4 has been entrapped. Using the carrier system, drug concentrations in the liver, spleen, lung, heart, and kidney were less than 5 μg per gm of tissue, whereas, with the dose-equivalent of free drug, these organ concentrations ranged from 5 to 15 μg per gm. This targetable drug carrier could provide a new method for the localized delivery and concentration of various water-soluble, chemotherapeutic agents.

Clinical Pharmacology - Phototherapy: It has long been known that certain porphyrins, notably hematoporphyrin, tend to accumulate in malignant tumors in higher concentrations than in normal tissue following systemic administration. Because of its very low toxicity and well-known ability to accumulate specifically in a large number of human tumors, hematoporphyrin is a preferred photosensitizing dye for clinical use.

Researchers (Dougherty, et al., 1978) have found that hematoporphyrin derivative is curative in treatment of various rodent tumors when the localized dye is activated by visible light near 630 nm delivered either from conventional light sources or an appropriate laser (photoradiation). Clinical studies of this technique on eleven different types of cutaneous and subcutaneous tumors have indicated that a very high response rate can be obtained with good therapeutic index (tumor/skin). Complete regression of tumor within the treatment field has been found in 90 percent of over 40 cases to date. The technique shows promise for treatment of chest wall disease recurrent following conventional therapeutic modalities. Response to photoradiation appears not to be compromised by previous surgery, chemotherapy, or radiation therapy. Both single and fractionated schedules of exposure to the 630 nm light are currently being investigated clinically.

Emphases and Projections

Identification of Drug-Induced Carcinogenesis: Various groups of cancer chemotherapeutic agents show carcinogenic potential in laboratory animals and in man. These include radioisotopes, immunosuppressive drugs, cytotoxic agents, hormones, and antimetabolites. At present, data on drug-induced malignancies in the human are sparse. Research effort will be emphasized in the areas of early diagnosis and prevention to seek precise data to assess the incidence of secondary tumors following prolonged drug treatment. Cancer chemotherapeutic agents will become increasingly important as the means to understand the mechanisms of oncogenesis. Since the exact amounts of drugs administered to patients are known, it is possible to obtain precise data regarding predictive value of short-term assays for transformation in culture and mutagenicity including chromosomal damage. These late effects include the induction of secondary cancers. Knowledge of parameters affecting such induction is of significant importance, since long-term survivals following chemotherapy do occur with many forms of human malignancy. Studies on mechanism of transformation through use of chemotherapeutic agents will allow for the discovery of new effective drugs which have reduced potential for producing secondary tumors.

As different conditions are added to therapeutic indications for a specific drug, new assessments must be made of risk-benefit ratios in the selection of appropriate drugs. Future research effort in this area will be pursued in the form of coordinated periodic evaluation and follow-up examinations of patient groups exposed to cancer chemotherapeutic drugs. In addition, there would be periodic monitoring of patients treated earlier for early signs of involvement with secondary tumors as a result of drug exposure.

Emphasis will be placed on research toward identification of biochemical mechanisms of drug-induced carcinogenesis. New drugs may be developed that are equally effective but noncarcinogenic and agents may be added to therapeutic regimens that would inhibit or block the carcinogenic action.

Transport and Selectivity of Anticancer Agents: Emphasis will be focused on modes of cellular uptake by drugs in order to better determine the natural selectivity of action of anticancer agents. More work is needed to clarify the relationship between the intracellular fate of a compound and the speed of its passage through the plasma membrane. It appears that in many cases plasma membrane passage is a rate-limiting step for intracellular conversion or binding. However, there may be situations in which the intracellular conversion or binding of a compound is the rate-limiting step and can, thereby, affect membrane passage. The latter possibility seems to apply for purines, pyrimidines, and their nucleosides. It is clear that the plasma membranes or cells and tissues vary greatly with respect to their permeability characteristics and that this variation needs to be clarified in future research efforts.

Pharmacological Control of Cyclic Nucleotides: The nucleotide cyclases and the cyclic nucleotide phosphodiesterases are complex enzyme systems having multiple receptor sites or multiple molecular forms. The various forms of these enzyme systems exist in specific cell types and can be differentially activated and inhibited by several endogenous and exogenous compounds. This selective alteration of specific forms of the nucleotide cyclases and cyclic nucleotide phosphodiesterases by pharmacological agents suggests the possibility of modulating the activity of these enzymes in individual cell types, resulting in a specific alteration of cyclic nucleotide concentration in certain cells. This evidence, together with the evidence that cyclic nucleotides have profound biological effects and may be involved in certain disease states, suggests that it may be possible to develop a new class of drugs whose pharmacological action is based on the specific alteration of the intracellular concentration of cyclic nucleotides in discrete cell types. Future emphasis will include increased studies in this area of cyclic nucleotides.

Enzyme Therapy: Considerable progress has been made in the development and testing of enzymes for parenteral chemotherapy. The biologic obstacles of susceptibility to proteolytic degradation, restricted distribution, and immunogenicity have limited the uses of these highly efficient and specific catalysts. Further advances require the development and selection of enzymes with properties specifically suited for a particular therapeutic use. These enzymes may require chemical modification, encapsulation, or immobilization on biocompatible matrices to improve their stability and decrease the immunogenicity. Directing the enzymes to extrahepatic sites is a much more difficult problem. Tumor-specific antibodies have a limited distribution in the host and therefore may not improve the effect of antitumor enzymes. Certain drugs and hormones with specific high affinity receptors on the target cells may be ideal agents to bind to soluble or immobilized enzymes.

Other Program Activities

Conference Support: The Drug Development and Pharmacology Program provided partial support for travel assistance for foreign invited speakers and for publication of the proceedings of the VI International Symposium on Chemistry and Biology of Pteridines in Relation to Chemotherapy. This conference included discussions on the occurrence, chemistry, metabolism, function, and chemotherapeutic aspects of pteridines. Information gathered in recent years on the mechanism of the chemotherapeutic effects of antifolates was correlated with emerging information on specific biochemical differences between susceptible and refractory cells.

Mass Spectrometry Facilities: Analytical and structural investigations of compounds and their analogs will play an increasing role in the area of cancer chemotherapy. The applications of mass spectrometry offer substantial advantages in terms of sensitivity and objectivity in studying problems of structure, biosynthesis, and drug metabolism of anticancer compounds.

Mass Spectrometry Facilities have been established with National Cancer Institute support at the University of Illinois and the University of Utah to provide an increasingly important resource facility for all grant-supported investigators in the Program needing such services.

DRUG DEVELOPMENT AND PHARMACOLOGY

SUMMARY BY SUB-CATEGORY
(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
SYNTHESIS & CHEMISTRY	84	$5,344	55	$3,915	139	$9,259
NATURAL PRODUCTS	25	1,546	16	1,018	41	2,564
SCREENING & EXPERIMENTAL THERAPEUTICS	17	1,078	7	425	24	1,503
PRECLINICAL TOXICOLOGY & PHARMACOLOGY	8	519	9	678	17	1,197
OTHER PRECLINICAL	5	424	4	236	9	660
MECHANISM OF DRUG ACTION	54	4,390	23	1,845	77	6,235
CLINICAL PHARMACOLOGY	1	100	3	234	4	334
PROGRAM PROJECTS	2	1,325	2	1,382	4	2,707
CONFERENCES	1	12	1	9	2	21
YOUNG INVESTIGATOR AWARDS	0	0	2	67	2	67
TOTAL	197	$14,738	122	$9,809	319	$24,547

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RADIATION PROGRAM

Description

The Radiation Program continued a steady rate of growth in fiscal year 1978 despite the inability to recruit an academic radiation therapist on sabbatical for the rotating Program Directorship for Radiation Therapy to complement the Program Director for Radiation Biology and Physics.

The Program can be resolved into components in a number of ways. As was often done in the past, the program can be viewed as composed of three segments of approximately equal size: traditional research grants, specialized low LET (linear energy transfer) Radiation Research Centers and high LET Radiation Research Centers. The following table illustrates another way of resolving the program into components:

Traditional Grants (R01's)

Component	% Dollars
Conventional Radiobiology	59%
High LET	16%
Hyperthermia	8%
Radiation Physics/Engineering	5%
Radiation Modifiers	4%
Radiotherapy	4%
Nuclear Medicine	4%
	100%

Program Projects (P01's)

Conventional Radiation Research	60%
High LET	40%

Interagency Agreements and Contracts

Conventional Radiation Research	13%
High LET	78%
Radiation Physics/Engineering	9%

Conventional Radiation Research Programs are equivalent to specialized Radiation Research Centers. These generally have biology, therapy, and physics components with one-half to two-thirds of the support going into biology.

As in past years, heavy program interest continues in high LET radiation research, which includes neutrons, protons, pions, alpha particles, and heavy ions. Substantial interest continues in the radiation community in hyperthermia and radiation modifiers, especially hypoxic cell sensitizers.

Research Accomplishments

High LET research continues to be a most exciting and most promising area in radiation therapy research. Presently the NCI is supporting four programs aimed at a cooperative clinical evaluation of fast neutrons in addition to one for protons, one for pions, and one for heavy ions.

The postulated advantages of various high LET radiations in therapy may be either physical (better dose distribution), biological, or a combination of both. Although a number of biological mechanisms have been suggested, the most commonly cited is the role of oxygen in cellular radiation damage. Essentially, tumors of appropriate size may have a core of lowered oxygen concentration. Oxygen is a radiation sensitizing agent, but more so for photons than for high LET radiations. Thus hypoxic tumors may be more susceptible to high LET radiations than to photons.

The four neutron programs are located at (1) Texas A and M under the clinical direction of the M. D. Anderson Hospital; (2) the Naval Research Laboratory under the clinical direction of George Washington University; (3) the NASA-Lewis facility under the clinical direction of the Cleveland Clinic; and (4) the National Accelerator Laboratory (Fermilab) outside of Chicago. Up to the present time, over 1,000 patients have been treated with neutrons in the United States in phase I and II studies. In addition, about 150 patients have been treated on cooperative clinical protocols (Parker, 1977) including cancers of cervix, oral cavity, pharynx and larynx, esophagus, and prostate.

Each treatment facility has utilized an existing accelerator originally designed for physics research. This approach was early recognized to have inherent problems because of lack of close proximity to major medical centers and lack of flexibility of available machine time appropriate for clinical usage. This approach also at least partially accounts for the rather disappointing accession rate at some of the facilities.

In the past year· the M.D. Anderson group has submitted to NCI a series of proposals and has been recommended for approval for funds to relocate their treatment facility from Texas A and M University to the hospital grounds in Houston. This will constitute the first U. S. medically dedicated neutron therapy facility. The first patient is expected to be treated by the spring of 1980.

Relative to the other high LET facilities, pilot studies are continuing with protons at the Harvard Cyclotron Laboratory under the clinical direction of the Massachusetts General Hospital (Gragoudas, 1977); with heavy ions at the Lawrence Berkeley Laboratory under the medical direction of the University of California, San Francisco (Castro, 1977); and with pions at the Los Alamos Scientific Laboratory under the direction of the University of New Mexico (Kligerman, 1977). Controlled clinical trials with pions are expected to commence in fiscal year 1979.

The program interest in hyperthermia continues to grow. Starting with evidence that cancer cells are more sensitive to elevated temperature than surrounding normal cells modern technology offers promise of carefully controlled whole body heating and carefully tailored local, deepseated tumor heating. These techniques alone or in appropriate combination with chemotherapy or radiotherapy offer fruitful fields for clinical research (Leith, 1977).

The area of radiation modifiers has experienced a renewed interest in recent years with development and availability of so-called hypoxic cell sensitizers (Hall, 1977). These drugs have an easier time gaining access to hypoxic areas of tumors than oxygen but otherwise mimic its radiation sensitizing effect. Substantial efforts now are going into investigating available hypoxic sensitizers and developing new ones with lesser side effects.

Emphases and Projections

With the three major areas of emphasis now being pursued, rich veins of research are clearly evident for the forseeable future. Assuming the promise in high LET radiotherapy stays bright, it is clear that at least a decade of work will be required for full exploitation. The prospects of hyperthermia and radiation sensitizers are also bright, but they are in an earlier stage of development.

RADIATION PROGRAM

(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
TRADITIONAL	72	$ 6,915	41	$ 3,397	113	$10,312
PROGRAM PROJECTS	17	13,446	6	6,334	23	19,780
CONFERENCES	0	0	2	201	2	201
YOUNG INVESTIGATORS AWARDS	0	0	1	33	1	33
RADIATION DEVELOPMENT	4	1,459	11	2,691	15	4,150
TOTAL	93	$21,820	61	$12,656	154	$34,476

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CANCER CENTERS PROGRAM

Description

The Cancer Centers Program, initiated in 1961, is designed to provide grants for the support and development of cancer programs which engage in clinical and basic research, search for and discover ways to improve the diagnosis and treatment of cancer patients, train an effective group of physicians and investigators for the future, and hasten the upgrading of cancer care in the community. The cancer centers have increased significantly in number and have diversified in function. A balanced combination of comprehensive and other types of cancer centers provides a national resource for the conduct of the full spectrum of cancer activities necessary to achieve the objectives of the National Cancer Program.

As a national resource, cancer centers provide a critical core of highly trained laboratory and clinical research personnel, physical facilities and equipment, and administrative structures necessary to generate new knowledge of cancer and accelerate the transfer of knowledge of improved cancer prevention, diagnosis, treatment, rehabilitation, and continuing care to health professionals and the general public in their surrounding communities.

There has been increasing emphasis on centers of broad scope which can provide a comprehensive, multidisciplinary attack on cancer problems. The National Cancer Act of 1971 and the National Cancer Act Amendment of 1974 stimulated this trend by providing for the establishment of additional cancer centers. Because they serve as foci for a variety of high-priority thrusts in the attack on cancer, these centers have assumed an increasingly important and visible role in the intensified strategy of the National Cancer Program.

The Cancer Centers Program develops, directs, and administers a program of core support grants for comprehensive and noncomprehensive cancer centers, evaluates the effectiveness of the Cancer Centers Program, coordinates program activities with related activities in other Divisions of the Institute, presents grant applications and provides special reports as required to the National Cancer Advisory Board, and maintains liaison with the appropriate Federal and non-Federal organizations, institutions, and scientists.

The Cancer Center Support (Core) Grant is the mechanism used to support those elements of a cancer center that are required for planning, development, evaluation, administration, and maintenance of an active and unified center to consolidate and focus cancer-related activities in a single administrative and programmatic structure. Through this mechanism, support is contributed to the stability of the center, to administrative and programmatic management of center activities, and to fiscal accountability and responsibility. It provides support for professional staff, centralized services and resources, and shared equipment. Research per se is not supported by the core grant except for small developmental projects which are limited to three years. Only a portion of a center's operational costs is furnished by these core grants. A major portion is supplied by combinations of individual research grants, clinical and basic program project grants, cancer control grants, clinical education and training grants, fellowships, contracts, and sources of support other than NIH.

Accomplishments

Proposals for cancer center support grants undergo scientific and technical peer review. The primary review for all CCSG's is carried out by the Cancer Center Support Grant Review Committee in the Review and Referral Branch of the National Cancer Institute. Important criteria are a record of cancer activities of high quality and an administrative organization that will promote and conduct a concentrated interdisciplinary attack on the cancer problem.

The cancer centers are divided into three categories: comprehensive, clinical, and nonclinical. The 19 centers which have been recognized as comprehensive by NCI have complied with or are in the process of complying with the ten characteristics established by the National Cancer Advisory Board as requisite for recognition as a comprehensive cancer center.

In response to requests for recognition as comprehensive cancer centers, on-site visits are conducted by special National Cancer Advisory Board-sponsored site visit teams which then make recommendations to the NCI Director as to what actions should be taken. To assist in this process, a formalized set of criteria for determining the current capabilities and potential for comprehensiveness of a center has been developed. With the help of selected representatives from the scientific community, a series of questions were drawn up relating to each of the ten NCAB characteristics of a center. This list of questions was revised and refined and used to develop an NCAB Site Visit Guide Book which is used as a guide by site visit teams at centers undergoing a review for comprehensiveness. In addition to looking at the centers requesting comprehensive status, an overall, thorough review of the existing comprehensive cancer centers, begun in 1977, is continuing. The data gathered during this process will establish a sound information base for evaluating the impact of the cancer centers on the National Cancer Program.

The Cancer Centers Program also initiated an intensive information-gathering activity at each of the cancer centers across the United States. With the help of a number of scientific consultants from the centers, a data collection document (the Cancer Centers Profile) was developed. At this time, 52 of the centers have completed the document, which was designed to capture administrative and fiscal information on individual cancer centers' operations and to identify funded projects determined to be under the cancer centers' control. When completed, this activity will provide a detailed data base--including scientific, administrative, and fiscal information--upon which to base an improved description of the cancer centers component of the National Cancer Program and of the individual centers themselves.

The Exploratory Grants Program has accomplished its primary purpose of supporting costs of planning for new centers and expansion, modification, or strengthening of existing centers. These exploratory grants have allowed institutions to do a careful analysis of the various alternatives available to develop a cancer program consistent with local needs and organizational structures as well as to contribute to the goals of the National Cancer Program.

Projections

During the 1979-1983 time period, the rate of Centers Program's expansion will decrease, and efforts will be directed toward consolidation and integration of the various program components.

The activity of establishing a detailed data base to provide a more complete description of cancer centers will be continued. Based on analyses of the capabilities of the various centers and the needs of the National Cancer Programs and the surrounding communities, efforts will be initiated to maximize the contributions of the individual centers and the network of centers.

Increased emphasis will be placed on enhancing and expanding the outreach activities of the centers. In particular, emphasis will be placed on the enhancement of community outreach efforts which transmit recent diagnostic and treatment research findings to professional and lay people who may not have direct affiliation with a cancer center.

Efforts will continue to encourage physicians located in community hospitals in areas surrounding cancer centers to consult with and relate to the center investigators who are in their specialty areas whenever practicable. Programs presently being developed, and some currently under way, are targeted to make the knowledge acquired by investigators in centers more readily available to both the professional and lay public. The expanded community outreach activities should contribute substantially to the tangible impact of the centers upon their surrounding populations through increased availability of consultation, professional education, and public information assistance.

During the 1979-1983 time period, management emphasis will focus on consolidation and integration of the various components of the Cancer Centers Program. Major activities to be conducted as part of this effort include specific planning, analysis, evaluation, and coordination activities. These activities will be directed toward completing a comprehensive plan for the Centers Program. This effort will focus particularly on: (1) refining the Centers Program objectives and criteria for evaluating the achievement of the objectives; (2) programming the activities necessary to integrate and consolidate the centers network; (3) updating the classification of and criteria for centers to more accurately reflect their roles in the network; and (4) establishing evaluation methodologies and procedures to continually assess the impact of the Centers Program.

Other Activities

Experience in the development of cancer centers has shown that supporting services relating to data management are essential.

To date, each of the comprehensive cancer centers has developed a statistical analysis, data management, and epidemiology program known as the Epi/Stat Program funded as part of the core grant. This program serves as a research resource for the individual researchers in the center. The programs offer consulting services and maintain data systems including the necessary computer software.

In 1976 a contract was funded for a Statistical Analysis and Quality Control Center at the Fred Hutchinson Cancer Center to develop a uniform Cancer Patient Data System to be participated in by each of the comprehensive cancer centers. Since that time a uniform data set has been developed, and the collection of patient data has begun, starting with patients that entered the system as of July 1, 1977. To date, data are being collected from a majority of the centers with the expectation that all comprehensive centers will be reporting within the next year. The first quarterly reports have been prepared for seven centers which were included in the first cycle of collection.

A Quality Control Program is an important feature of the data system and a constant effort is being made to standardize the data collected and control the quality of the data entering the system. To date, three regional seminars have been held to assist the centers in maintaining a high quality of data. More seminars are planned in the coming year as well as an evaluation program of submitted data.

CENTERS PROGRAM

(Dollars in Thousands)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
CANCER CENTER SUPPORT (CORE)	37	$34,337	27	$25,913	64	$60,250
EXPLORATORY PROJECTS	6	405	2	295	8	700
CANCER CENTERS PATIENT DATA SYSTEMS	16	1,580	1	70	17	1,650
TOTAL	59	$36,322	30	$26,278	89	$62,600

Description

The Cancer Research Facilities Construction Program was initiated in September 1971 with a public announcement of the availability of grant funds to create additional cancer research facilities. The essence of this announcement is set forth in the following paragraph:

> In accordance with the President's call for an expanded, intensified, and coordinated cancer research program, and under authority provided by the Congress in the fiscal year 1972 appropriation act, the National Cancer Institute initiated a program of grant-supported construction of cancer research facilities. The intent of this program is to create new physical resources for cancer research through Federal participation in the cost of new construction and renovation. Support may be provided for the construction of facilities such as basic research laboratories; clinical research facilities; animal facilities; and basic associated core, administrative, laboratory, and service space. In all instances, the facilities proposed must be intended for expansion of cancer research for at least 20 years. A purpose of this program, in addition to strengthening research capabilities at existing cancer centers, is to develop new strong multidisciplinary cancer efforts in regions of the country where they do not exist. Thus, in the consideration of applications some attention will be given to geographical distribution as well as to the relation of proposed construction to existing centers of excellent cancer research.

Justification of construction funds has been, and will continue to be, in terms of new cancer research programs and in the provision of safe facilities for accomplishing biohazardous cancer research. The primary review and evaluation of applications have been essentially scientific, considering such matters as scientific merit of the proposed program(s), the technical competence of the applicant institution staff, the intellectual environment of the applicant institution, and its scientific, fiscal, and administrative capabilities. In addition, other criteria have been considered, such as the location of the applicant institution, the applicant institution's role in the National Cancer Program, the promptness with which construction can be started, space requested commensurate with projected program scope, essential minimal facilities for those institutions with an undeveloped cancer research program, net space utilization of 60 percent or more, reasonable cost per gross square foot, and acceptable design criteria.

During fiscal year 1978, 29 construction grant applications were received and were reviewed generally by site visit teams. Following the site visits, parent review committees held additional deliberations. After the final evaluation by the National Cancer Advisory Board, 19 applications were recommended for payment. The recommended funding for these 19 applications was $28,335,314.

Additionally, a carryover obligation (from fiscal year 1977) on one grant totalled $947,434. Two administrative supplements were awarded for a total of $395,481. Thus, the NCI Construction Program faced approved funding requests of $29,678,229 after the initial evaluation of fiscal year 1978 applications.

The Construction Program's fiscal year 1978 budget was $12 million. The funds were awarded for the following 14 projects:

- Completion of previous (fiscal year 1977) awards:
  - Georgetown University (carryover)
  - University of Rochester (administrative supplement)
  - Yeshiva University (administrative supplement)

- Biohazard containment facilities (laboratories and animal housing):
  - American Type Culture
  - California Institute of Technology
  - Cornell University
  - Harvard Medical School
  - Michigan Cancer Foundation
  - Northwestern University
  - University of Alabama
  - University of Wisconsin

- Laboratories for basic cancer research:
  - Fred Hutchinson Cancer Research Center
  - University of California, Los Angeles.

- Expansion of neutron therapy space:
  - M. D. Anderson Hospital and Tumor Institute.

Eight approved applications were not funded because sufficient NCI funds were not available.

Recent Accomplishments

The National Cancer Advisory Board (NCAB) has been concerned that many NCI-supported extramural animal facilities may be inadequate and unsafe. This fiscal year, the Research Facilities Branch has conducted a major study to define the extent of the problem. The results of this study are scheduled for presentation to the NCAB in the fall 1978.

CLINICAL CANCER EDUCATION PROGRAM

Description

Since 1948 the National Cancer Institute has encouraged improvements in the quality of education relative to cancer provided to physicians and dentists, the two health professions most concerned with the diagnosis and management of malignant diseases. Medical and dental schools were eligible to apply for grants to achieve a "coordination" of cancer teaching and to provide additional experiences for undergraduate students to expand their understanding of cancer in its basic and clinical aspects. In 1966, this grant program was revised to include stipends for graduate trainees in clinical oncology in appropriate specialties, and to promote educational activities relative to cancer for practicing physicians and dentists. In addition to medical and dental schools, schools of public health, cancer institutes, and major teaching hospitals affiliated with medical schools became eligible for these grants. In the interval between 1966 and 1975, grants were awarded to a total of 112 institutions, and more than 4,500 individuals received support for periods of training relative to cancer ranging from three months for undergraduate students to two or three years for graduate trainees who received instruction chiefly in medical oncology, surgical and gynecologic oncology, pediatric oncology, cancer pathology, and radiation therapy.

In 1974, following a general phase-out imposed on all training programs at the National Institutes of Health, a new program known as the Clinical Cancer Education Program was initiated to carry forward the objectives of the earlier programs, namely, to stimulate and expand multidisciplinary efforts in cancer education at the undergraduate, graduate, and continuing education levels so that physicians and dentists might deal most effectively with the clinical aspects of cancer. This new program, as did its predecessors, provides support by means of grants for selected faculty and staff, teaching equipment and supplies, consultants, and travel, but supports no trainees. However, undergraduate and graduate students may receive salaries for portions of time devoted to cancer educational experiences. A 15-member Clinical Cancer Education Committee reviews applications for these grants, visits applicant institutions, and advises on program needs and accomplishments. The major teaching activities supported by means of these grants include curricular review and analyses, development of core-curricula on cancer, cancer courses, establishment or expansion of multidisciplinary cancer teaching experiences such as conferences, seminars, clinical rotations, and electives, the development of teaching materials and aids, exposure to visiting consultants and to specialized cancer facilities, and periods of intensified education relative to cancer of varying duration. All of the activities for which support is provided must be multidisciplinary and all must be evaluated for their efficacy.

The first Clinical Cancer Education grants were awarded in 1975 to 51 institutions for a total budget of $5 million. In 1976, these grants were continued and 31 new awards were made possible by a budget of $7.8 million. In 1977, awards were made to 67 ongoing and 19 new and renewed grants to 84 institutions. The budget for fiscal year 1978 ($9.450 million) permitted awards of 50 ongoing and 35 new, supplemental, and renewed grants.

Accomplishments

Unlike research projects, the outcome of cancer education programs cannot be judged by the contributions published by grantees in scientific journals. Improvements in the scope and quality of cancer instruction, in the extent of multidisciplinary cancer teaching activities, in the numbers of undergraduate and graduate students seeking specialized periods of cancer instruction, and in the numbers of practitioners responding to educational offerings are described by all grantees in their Progress Reports. Ultimately, it can be assumed that these activities lead to improvements in the quality of care provided to cancer patients by students and practitioners who benefit from these experiences. Site visitors to applicant institutions have been impressed with the extent to which the goals of the earlier programs have been achieved.

The Clinical Cancer Education Committee has reviewed 54 applications during three meetings in 1978, and has visited 38 institutions. Progress reports received from 67 institutions were reviewed by members of the Clinical Cancer Education Committee at their meeting on October 5-6, 1977. Sixty-four reports were considered satisfactory, and letters indicating this were sent to the grantees. Further information was requested from three grantees and was submitted upon receipt to the reviewers. Progress Reports on 56 current grantees will be reviewed by the Clinical Cancer Education Committee at their meeting in November 1978; the balance were reviewed as part of renewal applications.

During fiscal year 1978, consultative site visits were made to 12 institutions by the Executive Secretary, sometimes accompanied by a consultant or a member of the Clinical Cancer Education Committee, for the purpose of explaining to unsuccessful applicants why their applications were disapproved or received priorities too low to fund. These visits have proved to be very useful; in almost every instance, subsequent applications were approved with higher priorities, although awards could not always be made due to budget limitations.

The series of workshops on graduate education in oncology initiated in November 1976 has proven to be very successful. A follow-up meeting to the Workshop on the Training of Gastroenterologists in Oncology was held in Bethesda in January 1978; a summary of the meeting with recommendations has been forwarded to the Training and Education Committee of the American Gastroenterologic Association and to the National Cancer Institute.

Following the Workshop on Graduate Education in Oral Oncology which took place in June 1977, a summary was prepared and distributed to all schools of dentistry, graduate dental training programs, and to selected dental associations in addition to the Workshop participants. The response to this distribution was favorable and numerous requests for additional copies were received.

In June 1978, a Workshop on Graduate Education in Medical Oncology drew together approximately 30 persons including directors of graduate training programs in medical oncology and representatives of other disciplines which participate in such programs, to seek consensus on the content, scope, and variability which these programs should have in order to be most productive. A summary of the Workshop will be prepared. A preliminary planning session for a Workshop on Graduate Education in Surgical Oncology was held on June 23, and the Surgical Oncology Workshop will take place September 5-6, 1978. Plans are also under way for a Workshop on Graduate Education in Pediatric Hematology Oncology. A preliminary planning session for such a meeting is scheduled for July 25, and the Pediatric Hematology Oncology Workshop will take place in late September.

Emphases and Projections

To study the need for the resumption of training for specialized clinical oncologists, particularly in the areas of medical oncology, pediatric hematology-oncology, radiation therapy, gynecologic oncology, surgical oncology, and cancer epidemiology, a contract was awarded in December 1975, to Geomet, Inc., Gaithersburg, Maryland. The study, which determined finite needs in four of these specialties for which such data were not readily available, was based on current and projected numbers of cancer patients of the types most appropriate to the specialties. The results of this study indicated that in 1977 there was a shortage of 2,175 medical oncologists, 31 pediatric hematology-oncologists, 644 gynecologic oncologists, and 1,320 surgical oncologists, based on agreed-upon average work-weeks for each specialty. For 1980 and 1985 the shortages will increase unless current supplies of such specialists are expanded.

These data have been discussed with the members of the Clinical Cancer Education Committee, and have been made available to grantees and to interested groups and associations. The data will guide the Clinical Cancer Education Committee members in their review of applications requesting support for graduate education.

The success of the workshops on graduate education in the medical specialties indicates a need for additional programs in other disciplines. In the coming year, workshops on at least two more medical specialties will be held -- one on graduate education in an oncologic subspecialty and one on the oncology content of residency training in a clinical specialty.

Other Program Activities

Coordination is maintained with the Training Branch, National Cancer Institute, with the Resources Branch, Division of Cancer Control and Rehabilitation, National Cancer Institute, and to a lesser extent with the Office of Cancer Communications, National Cancer Institute. Active participation is maintained in the activities of the American Association for Cancer Education and the American Cancer Society. Consultants to the Program include, in addition to the members of the Clinical Cancer Education Committee, numerous clinical oncologists throughout the country who are experts in cancer education; 24 such individuals have provided services to this Program in the past year.

CLINICAL EDUCATION

(DOLLARS IN THOUSANDS)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNTS
51	$5,353	35	$4,141	86	$9,494

RESEARCH MANPOWER BRANCH

Description

The Research Manpower Branch supports the training of scientists who will be the mainstay of the cancer research effort ten or fifteen years hence. Because no one can foresee the direction cancer research will be taking then, it is imperative that a broadly trained nucleus of investigators be maintained who can change their research interests as new leads develop and old specialties become obsolete. To that end, NCI supports research training in the scientific specialties composing the broad areas of cancer etiology and prevention, cancer detection and diagnosis, and cancer treatment and restorative care. The training may be in clinical or nonclinical specialties and may be in either basic or applied research. Three grant mechanisms are used to support research training, namely:

a) the Institutional Fellowship Award;
b) the Individual Fellowship Award; and
c) the Research Career Development Award.

The first two of these awards were created in 1975 by the National Research Service Act. Institutional awards are made competitively to qualified institutions to develop or enhance research training opportunities at the predoctoral or postdoctoral level. The applicant must have the staff and facilities for the proposed program. After the award is made, the institution's training program director is responsible for selecting the trainees and for administering the program. Residencies may not be supported by this program.

Individual fellowships are awarded only for postdoctoral research training in nonprofit insitutions here and abroad. An applicant for a postdoctoral fellowship must establish his acceptance by a preceptor and must present a detailed description of the research project which he will undertake as part of his research training. Residencies may not be supported by this program.

Research career development awards are not governed by the National Research Service Act. The purpose of these awards is to provide very promising young investigators the opportunity to devote full time to their development as competent independent cancer investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential.

Accomplishments

During the year, 1,292 trainees and fellows and 108 research career development awardees were supported. Their distribution in the three broad research training areas was as follows:

Institutional Fellowship Awards
(training grants)

	Predoctoral	Postdoctoral
Cancer Etiology and Prevention	323	329
Cancer Detection and Diagnosis	10	31
Cancer Treatment and Restorative Care	77	146

Individual Postdoctoral Fellowships

Cancer Etiology and Prevention	280
Cancer Detection and Diagnosis	20
Cancer Treatment and Restorative Care	76

Research Career Development Awardees

Cancer Etiology and Prevention	76
Cancer Detection and Diagnosis	10
Cancer Treatment and Restorative Care	22

During the last few years it has become apparent that many pre- and post-Ph.D. cancer research trainees lack a working knowledge of cancer pathology. With the intent of deepening their understanding of cancer and increasing the breadth of their research concepts, a workshop on the pathobiology of cancer was held in July 1978. A conference grant made to the University of California at Los Angeles in the name of Dr. Fred Fox supported the effort. Thirteen eminent oncologists, pathologists, and surgeons, presented an excellent summary of disease processes to a group of 80 NCI individual postdoctoral fellows and pre- and postdoctoral trainees. The results of the workshop are being evaluated. If the evaluation is favorable, it may be repeated in two years.

Some of the notable research accomplishments in the past year by postdoctoral fellows, trainees, and research career development awardees include the following:

A postdoctoral trainee, Terry Yu, has designed and synthesized new organic compounds which improve organ imaging in the diagnosis of cancer.

A new assay for transformation-defective viruses has been developed by Dr. D. J. Fujita as a result of his hybridization studies with DNA specific for the "sarcoma" gene of the avian tumor virus. This is a step towards understanding carcinogenesis.

A predoctoral trainee, M. Pike, has delineated the effect of murine neoplastic factors on the immune response. The factors are low molecular weight entities which inhibit in vivo macrophage accumulation and in vitro chemotaxis, but have no effect on polymorphonuclear leucocyte migration. It is believed that these factors protect neoplasms from immune destruction.

During chemotherapy for melanoma, it has been shown that neither nitrosoureas nor dimethyl-triazeno-imidazolo-carboxamide are immunosuppressive. Because the cellular immune response to tumors may be of considerable importance in determining the outcome of tumoricidal chemotherapy, these results suggest a particular therapeutic value for these agents.

A model has been developed using human cells which will be crucial in future experiments on tumorigenic mechanisms. Human cell hybrids derived from malignant and nonmalignant cells expressed many of the transformed properties of the malignant parent, but had no apparent tumor-producing ability. Because these cells show a lack of density-dependent inhibition of growth, a lowered requirement for serum growth factors, lectin agglutination, and anchorage independence, none of these well-known characteristics of cancer cells endow a cell with tumorigenic potential, alone or in concert.

Emphases and Projections

A reliable and accurate estimate of future research manpower needs may be impossible to achieve, given the variables of long-term changes in the magnitude of research support, the constantly changing direction of future research emphases, and the technological limitations inherent in research manpower estimates. A number of cancer research manpower need estimates have been made during the last five years, including those done by various professional societies, the National Cancer Institute Cancer Research Training Committee, etc. In short the sum of these estimates *in toto* is to identify as shortage areas virtually all the scientific specialities relating to cancer, i.e., radiology, oncology medical physics, pharmacology, toxicology, epidemiology, pathology cancer biology, carcinogenesis, immunology, etc. These estimates appear to be highly subjective in methodology. In the meantime, we have adhered to the Cancer Research Training Committee's advice in its 1971 report that "The eventual solution of the cancer problem will require the sustained labors of the broadest possible collection of experts in every area of biomedical science."

At the recommendation of the NCI's Research Manpower Review Committee, a conference of training grant program directors is being planned for fiscal year 1979. The purpose of this meeting is to address common problems in the research training area relating to predoctoral training, postdoctoral clinical research training, the need for nonresearch cancer training, etc.

RESEARCH MANPOWER PROGRAM

(DOLLARS IN THOUSANDS)

	NONCOMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
INSTITUTIONAL FELLOWSHIPS	92	$12,882	25	$2,265	117	$15,147
INDIVIDUAL FELLOWSHIPS	145	1,829	194	3,143	339	4,972
RESEARCH CAREER DEVELOPMENT AWARDS	98	3,415	12	362	110	3,777
RESEARCH CAREER AWARDS	8	240	0	0	8	240
TOTAL	343	$18,366	231	$5,770	574	$24,136

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